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# A BIBLIOGRAPHICAL SOURCEBOOK OF COMPRESSED AIR, DIVING AND SUBMARINE MEDICINE

## VOLUME III

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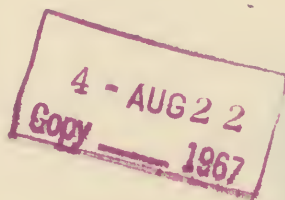


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# PREFACE

THE first volume of *A Bibliographical Sourcebook of Compressed Air, Diving and Submarine Medicine*, published in February 1948, constituted a reference source to the literature in medical problems of diving, compressed air work and submarine operations from the beginning to 1 January 1946. Volume II of the Sourcebook constituted an analysis and review of pertinent unclassified reports and documents as well as published books, monographs and papers published between 1 January 1946 and 31 December 1951.

The reader will find that the contents of the present volume have been dealt with consistently with the same policies that prevailed in assembling the first two volumes. As in the case of the first two volumes, the observations, conclusions and opinions of the research workers and other authors have been set forth briefly and all aspects of controversial issues have been considered. In arranging and classifying the material we have been guided by our judgment as to research trends and areas of special pertinence and importance.

In the present volume the coverage has primarily extended from 1 January 1952 to 31 December 1961. In areas of particular significance and in fields where rapid advances have been made, such as pressure physiology and hyperbaric oxygen therapy, we have extended the coverage up to the end of 1964.

With new developments in engineering science since Volumes I and II were published, there have been associated changes in the scope and emphasis of submarine medicine. These changes are reflected in the table of contents of the present volume. Many problems have been solved and with these solutions has come a shift in interests and research focus.

## ARRANGEMENT AND STYLE

Readers familiar with Volumes I and II of this Sourcebook will recognize that in the present volume the classification, arrangement and style conform to the conventions observed in the first two volumes. Each entry has been assigned a serial number which is used in the index of authors and in the text to identify the reference.

As in the previous volumes all journals and handbooks from which references have been taken are cited in a list given separately at the end of this volume. The arrangement of these items is in alphabetical order of their abbreviations, followed in each case by the full name of the publication and most recent place of publication. The system of abbreviations continues to conform to *A World List of Scientific Periodicals* published in the years 1900–1950, 3rd edition, New York and London. We have retained this system for the sake of consistency from volume to volume.

In the present volume there is no index of sources for unpublished reports. The reader may use the index of such sources on pages 362–364 of Volume II.

The present volume was prepared under contract Nonr 1134 (04), NR 102–527 between the Office of Naval Research and the Medical College of Virginia. It is desired to thank Dr. Leonard M. Libber, Head of the Physiology Branch, Office of Naval Research for his encouragement, advice and support. It is our privilege to express our appreciation to Dr. R. Blackwell Smith, Jr., President of the Medical College of Virginia and to the Staff of the College. We wish to record our gratitude to Mr. L. Daniel Crooks, Comptroller of the Medical College of Virginia and his staff.



We particularly wish to thank Captain G. J. Duffner, (MC) U.S. Navy, presently medical officer to the Commander-in-Chief, Atlantic Fleet. We were encouraged to undertake the preparation of this third volume largely through the initiative of Captain Duffner, who in all of the phases of this project has helped and advised us. Captain Duffner's interest in this work has been essential.

We express our appreciation to Captain Joseph P. Pollard, (MC) U.S. Navy, Director, Research Division, Bureau of Medicine and Surgery, for his ongoing interest and support. Thanks are also expressed to Captain Robert D. Workman, (MC) U.S. Navy, and Captain Jack Kinsey, (MC) U.S. Navy for their scientific and technical advice as well as for making available to us their personal reference files.

We owe a debt of gratitude to Dr. Christian J. Lambertsen, Department of Pharmacology, University of Pennsylvania School of Medicine, for technical and scientific suggestions as well as for his generosity in giving us access to his reference lists on oxygen.

We desire to thank Lieutenant Lawrence R. Raymond, (MC) U.S. Navy, Naval Medical Research Institute, Bethesda, Maryland for reviewing the sections dealing with cold. Thanks are expressed to Surgeon Captain F. P. Ellis, OBE, M.D., FRCP, Royal Navy Corps, for supplying reports and references from the British Admiralty. We are particularly grateful to our colleagues in the Royal Navy for this outstanding example of international cooperation.

Most of the work of collecting and abstracting the literature found in this volume was carried out at the National Library of Medicine, Bethesda, Maryland. We wish to thank Dr. Frank B. Rogers, then Director of the Library, for his helpfulness in placing the facilities of the library at our disposal for a period of about four years.

Among the many members of the library staff who have helped us we wish especially to offer our thanks to Mr. Edward A. Miller, Chief of the Reference Section.

We wish to thank Mrs. Mabel D. Clark, Librarian, Naval Medical Research Institute, Bethesda, Maryland for making the resources of her library so readily available to us.

We have pleasure in according thanks to Dr. William D. Blake, Head of the Department of Physiology, School of Medicine, University of Maryland, for his encouragement and for providing space for some phases of the study. Thanks are also expressed to Captain Herschel C. Suduth, (MC), U.S. Navy, Commanding Officer, Naval Medical Research Institute, and Captain Edward L. Beckman, (MC) U.S. Navy, Head, Department of Physiology, Naval Research Institute, for their sustaining concern.

Finally we wish to offer our sincere thanks to Mrs. Minna L. Hamner and Mrs. Mary Ita Greenbaum for the many hours of diligent effort which they gave in making ready the manuscript of this volume for the press. For this devoted work on the manuscript requiring such close attention to detail, we are deeply indebted.

The opinions and assertions contained in this volume should not be construed as official or necessarily reflecting the view of the Department of the Navy or the Naval Service at large. We hope, however, that we have accurately conveyed to the reader the substance and main advances in the fields of compressed air, diving and submarine medicine.

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# Technical Procedures and Research Apparatus in Compressed Air, Diving and Submarine Medicine

## I. GENERAL STUDIES IN SUBMARINE MEDICINE

The changing pattern of submarine medicine has been reported by Alvis (1) 1958. The advent of nuclear-powered submarines has greatly enhanced the scope and effectiveness of submarine operations and has consequently altered the medical submarine problem. Offshore may be the safest place during attack and exposure levels for most crew members may be less than for many people in situations not ordinarily classed as hazardous. Alvis reviews the physical and psychological screening procedures emphasizing that personality evaluation may be difficult to standardize. Such evaluation, however, is of great importance and especially in nuclear-powered submarines where there may be longer periods of isolation than in other craft. Since submarines operate in all climates it is essential that the environment be adjusted by air conditioning. Many or most of the old submarine medicine problems require and have received re-investigation within the new frame of reference of the nuclear-powered vessel. There are unsolved problems which challenge investigation for the future.

On the same general subject Ebersole (9) 1958, has outlined three important areas in which nuclear propulsion has added to the scope and depth of submarine medicine: 1) the environment of the true submersible vessel, capable of prolonged submergence, must be carefully controlled; 2) there must be strict radiation control for in-port periods during the time when the reactor shield may be open to admit workmen;

3) the submarine medical officer has become an assigned crew on board. The main problems of environmental control are the provision for a continuous supply of oxygen, the continuous removal of metabolic products such as carbon dioxide, and three, the prevention and removal of any toxic substances released to the boat's environment. Carbon monoxide problems on fleet type submarines arose from diesel fuel combustion, but on the nuclear reactor boats the principle source is cigarette smoking. The total safe concentration of carbon monoxide has been set at 100 ppm. Radon gas originating from luminescent radium-markers poses another problem in closed submarines on long submergence. This gas level is recorded as a rise in beta activity after submergence: it rises to 10 counts per minute per cubic foot after four days. Radiation problems are a potential source of difficulty and therefore radiation surveillance must be rigidly maintained. If contamination occurs the situation is serious because the closed atmosphere allows for little dilution of air-borne radiation. Also there is insufficient space for decontamination. In addition, the proximity of the living quarters to the reactor can pose a hazard. Submariners' work allows no possible off-site recuperation from exposure and air recirculation means that there would be a rapid spread of air-borne radioactivity from one spot to another.

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### III. PRESSURE CHAMBERS

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# Special Anatomy, Physiology and Biochemistry of Compressed Air, Diving and Submarine Medicine

## I. PHYSIOLOGICAL EFFECTS OF RAISED ATMOSPHERIC PRESSURES

### A. HEART AND CIRCULATION

It has generally been found that exposure to compressed air for long periods causes no enduring alterations in blood pressure or cardiac function. Thus Amorim (236) 1957, found only minor variations in the electrocardiogram of 20 subjects exposed to pressures of 10.7, 21.4 and 29.4 psi. It was found that the rhythm became less frequent in 93.5 percent of the cases and the P-R interval was lengthened in 74.06 percent. There was a higher respiratory frequency in 81.81 percent of the subjects.

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### B. RESPIRATION

Earlier studies on the effects of raised atmospheric pressure on respiration have indicated that repeated exposure causes an increase in vital capacity. However, more recently there has been doubt as to whether this occurs or if it does, whether there is more than a slight change. Studies on human subjects have shown that there may be an increase in the breath holding time and a slowing of the respiratory rate.

Buhlmann (240) 1963, has examined respira-

tory resistance with hyperbaric gas mixtures. Studies were made on male volunteers on the respiratory response to different gas mixtures. The mixtures used were helium ( $90 \pm 3$  percent) plus oxygen at 9.7 atmospheres, nitrogen ( $90 \pm 3$  percent) plus oxygen at 19.4 atmospheres and argon ( $90 \pm 3$  percent) plus oxygen at 29.0 atmospheres. Each subject was tested twice. It was found that as the depth increased the flow resistance increased also. The highest increase was for argon and oxygen and the lowest for helium and oxygen. The respiratory work was increased as the depth increased, being highest for argon and oxygen and lowest for helium and oxygen. Hesser and Holmgren (241) 1959, have also examined the effects of raised barometric pressures on respiration in man at pressures up to four atmospheres. These investigations were carried out on eight healthy subjects at rest in a recompression chamber. The independent effects of changes in inspired oxygen and nitrogen pressures were studied by comparing data obtained on air, 100 percent oxygen and five percent oxygen in nitrogen at various ambient pressures. Breathing air with increasing ambient pressure caused the respiration to become progressively slower and deeper whereas at four atmospheres the effective alveolar ventilation was slightly increased. At four atmospheres there was an average increase of 33 percent in the tidal volume, an average decrease in the respiratory rate of 27 percent, an increase in the respiratory minute volume of ten percent and an increase in the functional dead space/tidal volume ration of nine percent. There was no

demonstrable change in the expiratory reserve volume, or in the functional dead space and respiratory exchange ratio. The authors provided evidence that the respiratory changes were caused by the combined effects of increased oxygen tension and of breathing resistance due to increased gas density. Thus nitrogen at high pressures up to 3.8 atmospheres exerted little if any depressant action on respiration. Mead (243) 1956, has reported that exposures to increased ambient pressures increases the inertance of the lungs roughly proportionally to the ambient pressure, suggesting that inertance as measured was predominantly of the gas stream.

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## II. PHYSIOLOGICAL EFFECTS OF DECOMPRESSION

### A. PHYSIOLOGY OF BUBBLE FORMATION

Reference may be made to a report by Bishop, Walder and Van Liew (251) 1964, on the exit of oxygen and carbon dioxide from gas pockets during compression to 2 and 4 atmospheres. These authors have pointed out that the accepted treatment for decompression sickness is recompression which not only reduces the size of bubbles, but presumably facilitates their reabsorption as well. Assuming that large subcutaneous gas pockets are analogous to bends bubbles the authors studied carbon dioxide and nitrogen in rats after compression to 2 and 4 ATA. Compression at first increases the partial pressure of pocket gases. The  $P_{O_2}$  quadrupled with 4 atmospheres, but carbon dioxide left so rapidly that  $P_{CO_2}$  never reached the predicted level. After two hours compression the pockets reached a new steady state with  $P_{O_2}$  and  $P_{CO_2}$  only slightly higher than controls, demonstrating that these levels of compression with air exert minimal effect on tissue  $P_{O_2}$  and  $P_{CO_2}$ . The early exit of oxygen and carbon dioxide causes a bonus decrease in pocket volume and increases the fraction of nitrogen in the pocket which aids nitrogen absorption. At 4 atmospheres the volume decrease is about seven percent giving seven percent increase of  $FN_2$ .

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## B. SATURATION AND DESATURATION OF GASES IN THE BODY

Duffner and Snider (262) 1958, have studied the effects of exposing human subjects to compressed air and helium-oxygen mixtures for 12 hours at pressures of 2 to 2.6 atmospheres. Five Navy divers aged 21 to 34 years were exposed for 12 hours in a recompression chamber to increasingly greater pressures. The pressure in all cases was reduced at a rate of 25 feet per minute (11.12 pounds). The exposures were performed first while breathing compressed air and then later while breathing 80 percent helium and 20 percent oxygen. Greater exposures were tolerated with the helium-oxygen mixture than with air. The differences amounted to pressures equivalent to 3, 4, 6, 10 and 14 feet of sea water. Data on helium elimination disclosed that a large fraction (over 50 percent) of the dissolved helium is contained in a tissue component which desaturates very rapidly (half-time 1.5 to 5 minutes). The existence of a slow component (half-time 95 to 115 minutes) appears likely. The use of helium-oxygen mixtures in mixed gas SCUBA and the utilization of a single mathematical expression to compute decompression stops are considered feasible by the authors.

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### C. FAT AND WATER CONTENT

Reference may be made to this subject in Volume II of this Sourcebook and to the references listed below. It has been pointed out that fats and water are so distributed in the body that during saturation much of the nitrogen absorbed by fat diffuses from the body fluid. During decompression following partial saturation, the diffusion of nitrogen from the rapidly saturating body fluids into slowly saturating lipoids and fats tends to equalize the partial pressure of nitrogen in the different tissues of the body. Following brief exposures to very high pressures the fat acts as a nitrogen absorbent during decompression and acts as a buffer against bubble formation in the blood stream. It has been suggested that obese subjects with adequate blood supply and circulation should be better suited for short exposures in compressed air than lean men.

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## III. PHYSIOLOGICAL EFFECTS OF LOW OXYGEN TENSIONS OF ENVIRONMENTAL AIR

### A. LOW OXYGEN PERCENTAGES WITHOUT DECOMPRESSION

#### 1. SPECIAL SENSES

Conditions of hypoxia have been shown to result in a deterioration of functional acuity of the special senses. Although modern oxygen generating equipment in the submarines now obviate or minimize the hazard of reduction in oxygen percentage available to the submarine personnel, hypoxia problems may be a danger to divers using self-contained underwater breathing apparatus. There is, in general, never a problem for divers using an air supply from the surface, unless gear failure occurs. Experimental studies of the effects of hypoxia at ambient pressures still remain of interest.

Of interest are the effects of changes in arterial oxygen tension upon cochlear microphonics. Wing, Harris, Stover and Brouillette (295) 1953, have found in some cats that a reduction of arterial oxygen, from an average possible maximum value of 14.1 volumes percent to six to nine volumes percent, is accompanied by a definite although reversible depression in microphonics. The effectiveness of less severe degrees of hypoxia in reducing microphonics in cats was variable in the several animals used. This was explained in part by variability of circulatory adjustments and incidental changes in arterial carbon dioxide. The percentage fall in microphonics during hypoxia was unrelated to the initial magnitude of the cochlear response at the moderate levels elicited in this investigation. Complete recovery of microphonic output followed arterial concentrations as low as two to three volumes percent maintained for as long as about one-half hour. There was no instance of complete recovery after hypoxia of sufficient severity to lower arterial oxygen significantly below two volumes percent with arterial oxygen tensions below three volumes percent. There was a direct relationship between the depression of arterial oxygen and the time required to reach maximum recovery. When the reduction in microphonics during hypoxia



exceeded 80 percent, subsequent recovery upon termination of hypoxia was reduced and its temporal course was greatly prolonged. The authors found that no more than eight to nine seconds need elapse between the inhalation of oxygen in room air and a significant increase in microphonics already depressed by hypoxia. Cochlear microphonics were found to be reversibly reduced by inspiration of carbon dioxide in oxygen or air in concentrations between 5.2 and 25 percent.

Davis, Tasaki, Smith and Deatherage (286) 1955, have studied cochlear potentials after intracochlear injections as well as anoxia. They injected small quantities of salt solution into the scala media of the basal turn in the guinea pig while recording the endolymphatic DC potential through the injection pipette. Simultaneously they recorded the cochlear microphonics (CM), the action potential (AP), and the summing potential (SP) in response to 5000 cycles per second tone pips, recorded from other intracochlear electrodes. Injections of 0.2 cmm of artificial endolymph (with high potassium and low sodium) had little or no effect. Artificial perilymph containing sodium and potassium in the usual tissue fluid ratio was toxic but it affected CM much more than DC. Larger injections and complete perfusions of the scala media were complicated by probable mechanical injury. They depressed AT, CM and DC, but low potassium solutions were relatively more injurious than those with high potassium. Cocaine depressed CM and AP but not DC. It was found that cessation of respiration abolished AP and considerably reduced CM and DC. Following a single gasp, DC regularly returned promptly from less than 50 percent back to its full normal value. The increase in DC occupied less than three seconds and paralleled the familiar revival of CM and AP. These results suggested to the authors a more immediate dependence of the endolymphatic DC potential on an oxidative mechanism than on ionic concentration differences. The summing potential was greatly affected in complicated fashion by anoxia as well as by ionic changes, but was small or absent when the cochlea was presumably most normal.

Studies of the effects of oxygen lack on cochlear potentials have also been carried out by Fer-

nández (287) 1955, Fernández and Alzate (288) 1959, and Konishi, Butler and Fernandez (290) 1961. In their first paper these authors induced asphyxia in guinea pigs and cats to determine the survival time, recovery time and revival time for cochlear microphonics (CM) and action potentials (AP). Two phases of CM were identified. On the basis of the rapid decline of the fast phase a high metabolic rate of the hair cells was inferred. Lack of dependence of this decline on stimulus intensity suggested equal oxygen requirements among the hair cell population. The short survival time of AP supported the view that the cochlear nerve has a high metabolic rate, close to that of the central nervous system. A definite dependence of the survival time of AP upon stimulus intensity indicated that there are groups of fibers with different oxygen requirements. A short recovery time of CM reflects the rapid rate of physical chemical reconstruction of the hair cells after initial recovery of responses, a full recovery was generally observed and occasionally there was overshooting. Repetitive asphyxia usually produced cumulative depression, probably due to irreversible changes. The recovery time of AP was of the same order of magnitude as that of the central nervous system. The recovery time of AP varied as did survival time with stimulus intensity. This was considered by the author to represent different rates of physico-chemical reconstruction among the primary cochlear neuron population. AP recovered fully and as a rule exhibited overshooting, at times as high as 75 percent over normal. Fibers with lowest threshold were characteristically the most sensitive to repeated asphyxia. It was found that survival/revival time for asphyxia could not be determined since the animals died within seven minutes. Fernández and Alzate found that cochlear responses depended upon an adequate oxygen supply. Neural components ( $N_1$  and  $N_2$ ) were most sensitive. Their survivals were 90 and 60 seconds, respectively when asphyxia or fulminating anoxia was imposed while cochlear microphonics ( $CM_1$ ) survived about 300 seconds. Depressions of  $CM_1$ ,  $N_1$  and  $N_2$  seem to be related to those chemical reactions underlying the generation of energy. The recovery of cochlear responses after a bout of oxygen deprivation followed a definite order:



CM<sub>1</sub> recovered within ten seconds; N<sub>1</sub> lagged CM<sub>1</sub> by a few seconds; N<sub>2</sub> was the last potential to reappear. Recovery seemed to depend upon factors such as duration and degree of oxygen lack, and was probably related to the reconstruction properties of the generators of cochlear potentials. The authors found that exposures to asphyxia repeated at one hour intervals produced an apparently permanent depression of both cochlear microphonics and neural components, provided the duration of each bout was at least three minutes. In these guinea pigs no changes in their inner ear structure were found after hemotoxin eosin stain and study with light microscopy. Unanesthetized guinea pigs exposed several times (30 to 45 minutes each) to gas mixtures of N<sub>2</sub> with 3 percent oxygen and kept alive for about six weeks, also revealed no histologic changes in the inner ear. Similarly the temporal bones of animals exposed once for a period of about two hours to the same gas mixture and kept alive for several days revealed no evidence of histologic change. Routine histologic methods such as hemotoxylin eosin stain and light microscopy were believed to be inadequate for detecting changes in the inner ear structures of animals with apparently permanent depression of cochlear responses induced by repeated exposures to anoxia. Chronic experiments suggested that this depression was a reversible phenomenon.

In the experiments of Konishi, Butler and Fernández, the anterior inferior cerebellar artery of guinea pigs was occluded as a device for interrupting the blood supply to the cochlea and thus producing anoxia. Durations of occlusion ranged from 1 to 60 minutes. Cochlear microphonics, summing potential, action potential and endocochlear potential were recorded before, during and after occlusion. Differential effects of anoxia upon the various potentials was observed, as well as the appearance of large negative DC potential in the scala media as anoxia progressed. For brief occlusion durations, the amplitudes of all potentials, except cochlear microphonics, became greater than normal soon after the blood supply was restored. Even for the longer anoxic periods, the summing potential and the endocochlear potential exhibited super normality during the recovery process.

To evaluate the role played by endolymphatic hyoxia on deafness, Mizrahy, Shinnebarger and Arnold (291) 1958 made continued recordings of oxygen availability, action potential and microphonics taken during asphyxia, chronic hypoxia and after loud sounds. Their results showed that hypoxia may play an important contributory role in temporary losses of hearing following loud sounds. The possible mechanisms of auditory trauma may be mechanical injury and acoustic vibrations inducing change in the permeability of the basilar membrane allowing ionic potassium to leak from the scala media and block hair cells and nerve endings. Hypoxia may produce diffuse reversible or irreversible changes not necessarily accompanied by obvious structural changes. A great variety of other bio-medical changes may be involved, such as variations of carbon dioxide tension, pH, and accumulation of metabolites. Mizrahy, Spradley, Zinovich and Brooks (292) 1961 found that intense sound, hypoxia and kanamycin increased the permeability of cochlear partitions.

In a study of the effects of environmental changes upon the cochlear response of the cat, Wing (294) 1962 used a sound stimulus of 4000 cycles per second of constant intensity to produce the cochlear response (CR). Completely reversible losses in CR were associated with hypercapnia (6.7 percent and 24 percent carbon dioxide in oxygen). This loss was not maintained during exposure, indicating that carbon dioxide may not have been acting directly upon the "electrical generators". Flooding the bulla with carbon dioxide and oxygen at room temperature caused a significant and reversible reduction in the CR in a matter of seconds. Production of hypoxia through tracheal clamping and low oxygen-nitrogen mixtures caused a reduction of arterial oxygen from 14.1 to 6 to 9 volumes percent, often accompanied by definite and reversible drops in the CR. Effects of minimal and moderate hypoxia on CR were variable. Proportional fall of CR was unrelated to the size of the initial response. The rate of fall varied with the percentage of final voltage decrement and complete recovery was possible after two to three volumes percent arterial oxygen for 30 minutes, but not below two volumes percent. If the CR dropped more than 80 percent

during hypoxia recovery was incomplete and prolonged. With less severe hypoxia recovery began during exposure and the CR was greater after the hypoxia than before. Recovery was significant within 8-10 seconds post-hypoxia. With the bulla flooded with nitrogen or oxygen at atmospheric pressure before clamping the trachea, it was found that the postmortem CR at the round window depends on the presence of oxygen. The author believed that postmortem CR was produced by aerobic chemical reactions and that no qualitative difference exists between reactions generating CR antemortem or postmortem.

Gisselson (289) 1954 has examined the literature on the effect of oxygen-lack and decreased blood pressure on the microphonic response of the cochlear, and has also himself conducted experiments on the nature of the cochlear potentials. He believes that cumulative evidence argues strongly for the view that cochlear potentials are intimately related to the activity of the hair cells, that is to say that cochlear potentials can be demonstrated only in the presence of intact hair cells. The amplitude of the cochlear potentials is decreased by oxygen lack as well as by extreme reduction in blood pressure. Oxygen lack produced by the administration of potassium cyanide, which inhibits cellular respiration but increases blood pressure, decreases the amplitude of cochlear potentials, the decrease varying roughly with the degree of anoxia. Oxygen deficiency caused by deprivation of air supply causes an initial decrease of the amplitude of the cochlear potentials and a simultaneous, transient slight fall in blood pressure. After one or two minutes the blood pressure increases and there is an accompanying further decrease in the amplitude of the cochlear potentials. Reintroduction of the supply of oxygen to the animal increases the blood pressure violently as well as the amplitude of the cochlear potentials. Blood pressure then gradually drops with a corresponding gradual decrease in the amplitude of the cochlear potentials. This biphasic decrease in the cochlear potentials suggests to the author that the potentials are made up of two factors, one sensitive to oxygen lack and the other to changes in blood pressure. The cochlear potentials are very sensitive to oxygen lack, about 30 seconds of de-

privation of air supply being enough to cause reversible injury to the cochlea, and two minutes deprivation being enough to produce irreparable damage to the organ.

Of interest is a paper by Rizzo and Cinquemani (293) 1959. This paper deals with the behavior of the oculo-cardiac reflex of dogs at sea level under conditions of hypoxia. The authors investigated the behaviour of the ocular-cardiac reflex in normal conditions and with reduced oxygen supply in animals anesthetized with chloralose. Pulmonary ventilation was continuously recorded during the experiments and the oculo-cardiac reflex elicited with gradually increased compression of the eyeballs by the imposition of weights from 100 gms. to a maximum of 1000 gms. Each compression lasted for 15 seconds with one minute intervals between. In some animals reflex exhaustability was examined by means of weights of 500 gms. imposed for ten second periods with ten second intervals only. Hypoxia was induced by low  $O_2$  mixtures ( $O_2$  9%,  $N_2$  91%). There is a straight line relation between heart rate slowing and the weight used to elicit the oculo-cardiac reflex. OCR positiveness is less evident during hypoxia than under normal conditions and the threshold is raised. Pulmonary ventilation always undergoes a decrease when the eyeballs are compressed under normal sea level breathing conditions while during hypoxia an increase is sometimes found.

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## 2. NERVOUS SYSTEM

Weller (334) 1959 reported the case of a SCUBA diver who used a cylinder accidentally filled with 99.5 percent nitrogen and 0.5 percent oxygen instead of air. He became unconscious after a few breaths and was rescued from the water about 30 seconds later. Artificial respiration by Schaefer's method was begun and  $O_2$  given shortly after that. About 20 minutes after the accident behavior similar to that seen in recovery from nitrous oxide anesthesia was observed. The level of consciousness rose to normal during the next 12 hours. Thirty-six hours after the accident the patient was discharged from the hospital and remained symptom free. The author recommended that all free divers using SCUBA gear breathe through the apparatus for a period of 60 seconds, observed by a companion, before entering the water. For other studies of the clinical aspects of cerebral anoxia, papers by Steigman (337) 1951 and Monrad-Krohn (332) 1956 may be consulted. Kasamatsu (321) 1952 has reported studies on the loss of consciousness induced by inhalation of nitrogen gas, and a paper by Malette (328) 1958 on cerebral anoxia resulting from hyperventilation may be consulted.

Blocking of synaptic transmission occurs in anoxia. Studies on oxygen uptake of the crayfish

Blocking of synaptic transmission occurs in anoxia. Studies on oxygen uptake of the crayfish cord and the effect of anoxia on synaptic transmission have been reported by Wiersma and Ramos (345) 1953. Synapses between the third root motor fibers and giant fibers were blocked irreversibly after 20-40 minutes in commercial

nitrogen. This type of block was shown to be like that caused by alcohol. Whether the synaptic region is more sensitive to anoxia in this species than the axone remains undecided. Observations have been made on asphyxial and postasphyxial changes in electrical responses of motor neurons to antidromic stimulation by Lloyd (387) 1953. In these studies asphyxia was produced by suspending artificial respiration, ventilation being restored immediately after complete conduction block was established, thus permitting study of the postasphyxial state. The initial change is a central depolarization commencing after a latent period of one minute. There is a severe loss of somatic after-potential. Thus the dendrites acquire the ability to carry two volleys in rapid succession. Changes appear to reach completion within approximately 30 seconds. There then follows a period of convulsive activity. There is fluctuation in somatic responsivity demonstrated by reciprocal amplitude changes in the responses of the axones and dendrites. Intermittent impulse discharge in ventral roots is seen; conduction block may develop slowly during the convulsions. There is frequently a definite instance when convulsive activity stops and rapid development of block begins. The recorded amplitude of the dendritic responses increases to a peak and then disappears. This peak represents a developing block and not an increased response. When fully established the asphyxial block is located at the junction of the initial and myelinated axone segments and is a depolarization or cathodal block. On restoration of ventilation a latency of greater than 20 seconds precedes the beginning of the postasphyxial change. The membrane potential recovers and overshoots the normal level within a few seconds. At a critical stage, motoneurons are capable of conducting impulses but again lapsed into block. New block is due to hyperpolarization and is anodal in type and somatic rather than axonal. Final recovery requires 20 minutes after the rapid transition from asphyxial block through normal to post-asphyxial, the motor neuron will upon re-asphyxiation pass through a new and completely asphyxial cycle. For other studies on asphyxial spinal cord potentials, papers by Kolmodin and Skoglund (325) 1959 and Van Harreveld and Biersteker (339) 1962 may be consulted. Van

Harreveld and Biersteker (340) 1964 have shown that oxygen lack causes an impedance increase of the spinal cord coinciding in time with the asphyxial potential which can be led off from the spinal gray matter against an indifferent electrode. After a circulatory arrest the latency of these changes is of the order of ten seconds. After ventilation of the preparation with nitrogen the latency is 20-25 seconds. An asphyxial transport of chloride was demonstrated, passing into the dendrites of dorsal horn neurons and accompanied by a volume increase of these structures. The electrolyte movement can account for the impedance increase by a loss of extracellular ions which are the main carriers of the measuring current. The observed ion movement, taken as an indication of depolarization, suggests to the authors that the asphyxial potential is due to dendritic depolarization, the cell bodies and axones acting as source. This explanation is supported by the much slower decline of the spinal asphyxial potential, as compared with that of a similar potential which can be led off from the cerebral cortex. The difference in the rate of decline reflects the much slower asphyxial depolarization of the somas of spinal neurons as compared with that of cerebral nerve cell bodies previously observed.

The sensitivity of a number of spinal cord structures to anoxia have been determined in the dog by Gelfan and Tarlov (314) 1953. Responses of neurons, as well as afferent inflow of impulses initiated in dorsal roots or peripheral nerves, were recorded from the dorsum of the cord. Reflex outflow in ventral roots was also recorded on the oscillograph or by observation of leg muscle responses or both. Interneuronal activity gradually ceases after a minimum latent period of about four minutes following either inhalation of 100 percent nitrogen or in the spinal animal, interruption of artificial respiration. The positive component of the interneuronal wave complex is always the first to be abolished and the last to recover. Intramedullary afferent fibers continue to conduct impulses for some 15 minutes longer. The slower conducting ones being more resistant to anoxia. Dorsal root impulses continue to arrive at the cord for an additional 15 minutes and conduction in peripheral nerves is retained still longer. Spinal reflexes are abruptly

abolished after about 2½ minutes at a time when some interneuronal activity is still present and probably relayed to higher centers. Ventral roots retain their ability to conduct for at least as long as dorsal roots. Vulnerability, degree and sequence in the cord, roots and peripheral nerves to aschemic anoxia is the same as in anoxic anoxia only when the ascending aorta is clamped in the respiring animal, thus causing complete ischemia of the cord. Incomplete ischemia alters the order and rate of abolition of function as well as recovery rate. A more complete report of differential vulnerability of spinal cord structures to anoxia was given by Gelfan and Tarlov (315) in 1955.

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### 3. MUSCLE

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### 4. HEART AND CIRCULATION

The diving environment holds many potential hazards for dangerous hypoxia. Cardiovascular responses are some of the most easily measured and can be very critical. A number of more general papers on cardiovascular responses to hypoxia may first be discussed. Johansen and Krog (402) 1959, have studied peripheral circulatory responses to submergence asphyxia in the duck. The changes in peripheral blood flow were indicated by measuring the venous pressure rise in a branch of the femoral vein when the main venous return was occluded. Electrocardiograms and arterial pressures were recorded simultaneously. As the animals dived there was an extreme bradycardia with only a small change in the arterial blood pressure. The slow drop in the arterial diastolic pressure during diving indicated a great reduction in the rate of emptying from the larger arteries. The peripheral blood flow, determined from the degree of venous return, was likewise found to be reduced. The authors concluded that diving induces a compensatory shutdown of the circulation through the whole limb. This explains the animal's ability to compensate for the extreme bradycardia in the maintenance of high systemic arterial blood pressure, thus securing an ample circulation to the brain during asphyxia. Durfee and Sturkie (382) 1963, have pointed out that the initial responses of many animals to anoxia are transient vasoconstriction, hypertension and tachycardia. All of these are attributable to chemoreceptor stimulation and are of short dura-



tion. These are followed by loss of vaso-motor control, vasodilatation and cardiac failure if severe anoxia is prolonged. These phenomena were studied by the authors in the domestic fowl by using the technique of artificial respiration by unidirectional airflow. Cyclic blood pressure changes observed in eupneic breathing were obliterated by this procedure. Relative constant blood pressure and heart rate were maintained for long periods with humidified room air administered at ventilation rates above 350 cc./min. At lower rates (145 cc.-250 cc./min.) the animals responded by hypotension. With intact innervation tachycardia occurred concurrently. Both responses were reversed by increased ventilation rate and were repeatable. Similar changes in blood pressure occurred after bilateral vagotomy and after transection of the spinal cord. Results indicated to the authors that in the fowl the resting heart rate and reflex changes in heart rate are mediated by the vagus nerve. An initial hypertensive response to anoxia does not occur and the anoxic hypotension observed does not involve the central nervous system. Beard, Alexander and Howell (356) 1952, investigated the effects of breathing various oxygen deficient gas mixtures on heart rate, respiratory rate, arterial pressure and pulmonary arterial pressure in intact closed-chest narcotized dogs. Breathing mixtures of 8.5 percent oxygen in nitrogen for 30 minutes consistently produced increases in heart rate and systemic arterial pressure in a number of animals but did not significantly alter respiratory rate. Pulmonary arterial pressure remained essentially unaltered in spite of a slight and somewhat variable increase in cardiac output. Short periods of breathing mixtures containing approximately six percent oxygen consistently caused increases in heart rate, respiratory rate, systemic arterial pressure and pulmonary arterial pressure in four animals. Breathing oxygen free gas until apnea occurred produced the well-known pattern of changes in the systemic arterial pressure with some qualitatively different responses in the lesser circulation. Study of cardiovascular effects of low oxygen mixtures upon dogs has also been reported by Gorlin and Lewis (395) 1954. In these authors' investigations, dogs were given mixtures containing 2.5-10 percent oxygen with arterial saturations ranging from 60 to below 20

percent. With 60 percent arterial saturation there was an immediate systemic vasoconstriction and hypertension and with time, a gradually incremental pulmonary vasoconstriction. There were no changes in cardiac output. When the oxygen saturation was less than 60 percent, but greater than 40 percent, cardiac output and work done were increased. Systemic hypertension persisted, but vasodilatation occurred. With oxygen saturation below 40 percent cardiac work and cardiac output were greatly increased with increased diastolic filling. With severe hypoxia (saturations below 20 percent) this state could be maintained for varying but usually short periods. Since coronary blood flow could not supply the necessary oxygen, oxygen lack accumulated, oxidative enzyme production eventually decreased and cardiac contraction deteriorated. A systemic hypertension was maintained. In studies of cardiovascular responses of fetal lambs in utero to hypoxia, Reynolds and Paul (429) 1958, have pointed out that bradycardia is a clinical sign of fetal distress. Experimental studies of these authors led to the conclusion that mild hypoxia may cause cardiac acceleration in fetal lambs. When the ewe was subjected to 13, 10 and 6 percent oxygen in the inspired air for periods of 20 minutes, changes in systemic blood pressure and heart rate of the fetus were determined. With 13 and 10 percent oxygen the fetal heart rate slowed, increased slightly or fluctuated. Diastolic pressure remained nearly constant but systolic pressure invariably increased, indicating increased cardiac output. On six percent oxygen the fetal heart rate slowed, blood pressure declined and the pulse pressure decreased, but not invariably so. When the fetal blood pressure fell, heart rate was always slowed. The results indicated to the authors that heart rate alone was not a reliable criterion of fetal distress. The oxygen tension associated with fall in blood pressure and usually heart rate was 10 mm. Hg or less. Heart rate was affected when oxygen tensions were between 10 and 30 mm. Initial or early cardiac slowing could be inhibited by injection of atropine into the fetus. A further study on animals is that reported by Korner and Edwards (406) 1960, who found that mild degrees of hypoxia produced an increase in ventilation in the rabbit without eliciting a detectable

circulatory response. The early circulatory effects consist of bradycardia, a rise in main arterial blood pressure and a fall in cardiac output, indicating a predominantly systemic vasoconstriction. The magnitude of the bradycardia and rise in arterial pressure were related to the fall in arterial saturation. Atropine or vagotomy reduced or abolished the bradycardia, but greatly accentuated the rise in systemic blood pressure. Denervation of the carotid baroreceptors and chemoreceptors almost completely abolished the bradycardia and diminished the rise in systemic arterial blood pressure.

For more comprehensive papers dealing with the effects of hypoxia upon cardiovascular function, reference may be made to Daly and Scott (369) 1963; Fishman, McClement, Himmelstein and Cournand (388) 1952; and Russek (431) 1962.

Several papers on the effects of hypoxia on myocardial function may be discussed: the reader may wish to consult a review by Kardesch, Hogancamp and Bing (404) 1958, dealing with the survival of excitability energy production and energy utilization of the heart under conditions of anoxia. Cardiac excitability is most vulnerable to hypoxia, energy production and energy utilization survive longer. Webb and Hollander (442) 1956, have studied depression of atrial metabolism in the rat as produced by anoxia. There was a reduction in contractility associated with changes in the electrical properties of cell membranes. The most marked result was a shortening of action potentials due to more rapid repolarization rate. Changes in conduction rate were generally independent of potential changes but were related to increased latent periods induced by metabolic depression. All of these effects were mainly or completely reversible. In virtually intact animals with separately perfused carotid arteries, Cross, Rieben, Barron and Salisbury (366) 1963, found that an arterial  $P_{O_2}$  below 40 mm. Hg (about 75 percent oxygen saturation) caused edema of the heart muscle. However, the contractile strength and performance of isolated hearts were compromised severely when the arterial  $P_{O_2}$  had fallen below 15 mm. Hg (about 25 percent saturation). The acute circulatory crisis occurring when the arterial oxygen saturation fell below 80 percent was con-

sidered not to be caused by impairment of the heart muscle itself but by reflexes from the carotid artery. Even when the oxygen saturation of systemic arterial blood had fallen as low as 50 percent, this did not cause heart failure as long as the carotids were perfused with blood of normal oxygen. Severe heart failure occurred when the blood in the carotid arteries was moderately hypoxic ( $P_{O_2}$  below 50, saturation below 80 percent) while the rest of the circulation was fully oxygenated. Studies on blood and cardiac muscle have been carried out by Moulder, Hager and Eichelberger (420) 1961, who rendered dogs under ether anesthesia anoxic by total occlusion of the vena cava for periods of 10 minutes. A recovery period of approximately 30 minutes in air was allowed immediately thereafter. Following the recovery period blood showed an increase of serum potassium concentration but no increase in potassium red cell concentration. In the heart muscle the phase volumes were not changed, indicating no edema or dehydration of the muscle. Potassium and magnesium concentrations in the heart fibers were within normal limits, indicating that the architecture of the fibers had not changed and calcium concentrations were unmodified. Klein (405) 1961, found that embryonic chick myocardium anoxia had some, but small changes on cation movements in young embryos but the effects increased greatly at older ages. At different levels of cardiac work in the open-chest anesthetized dogs, Feinberg, Gerola and Katz (386) 1957, have examined the effect of increasing severity of hypoxemia on coronary flow and the myocardium. Coronary flow increased with increasing severity of hypoxemia at the same level of cardiac work. Arterial oxygen saturation diminished at a greater rate than venous oxygen, hence the A-V oxygen difference decreased with hypoxemia. The A-V oxygen difference remained independent of cardiac work and rate throughout the entire range of arterial oxygen saturations studied. Thus, at any given arterial oxygen saturation coronary flow was found to be the principal variable in the calculation of oxygen consumption over a wide range of work and rate. Oxygen consumption at isowork levels remained relatively constant over a large range of diminished arterial oxygen saturation but declined slightly in the



lower range. In the isolated rabbit heart Guz, Kurland and Freedberg (396) 1959, have studied the effects of acute changes in arterial oxygen content on coronary flow and myocardial oxygen consumption. Perfusion was performed with a 60 cm. water pressure head using Ringer-Locke solution containing varying concentrations of fully saturated bovine hemoglobin in equilibrium with a 3 percent carbon dioxide balanced air mixture at atmospheric pressure. Myocardial oxygen consumption was estimated from coronary flow and A-V differences across the heart. Oxygen capacities of perfusing fluids varied from 16–2 volumes percent, but were otherwise identical in pH, salt concentrations and viscosity. A shift from a high to a lower oxygen content fluid resulted in increased coronary flow; while the reverse changes were followed by decreased flow. Myocardial oxygen consumption remained constant with an arterial oxygen content above 2 volumes percent, but at this level fell reversibly by 15–30 percent. The authors concluded that changes in coronary resistance cannot be due to changes in arteriolar oxygen tension since this was atmospheric and constant throughout the experiment. Changes in oxygen tension at a more peripheral level in the vascular tree or the myocardium, with a reflex effect on the coronary resistance, or the accumulation of vasodilator metabolites were considered responsible for the changes observed in coronary flow. Increased coronary flow resulting from hypoxia may indeed be produced by release of adenosine from the myocardium under conditions of low myocardial  $P_{O_2}$  with the production of arterial dilation. Berne (358) 1961, has pointed out that adenosine is a potent coronary vasodilator which passes readily across cell membranes and is avidly incorporated into ATP by the isolated heart. Experiments were carried out on isolated cats' hearts perfused with Tyrode's solution in the intact heart of the open-chest cat. Nucleotide derivatives present in perfusates or coronary sinus plasma were adsorbed on charcoal, separated by column and paper chromatography and quantitated enzymatically. Adenine nucleotides and adenosine were not found in perfusates or blood under control or experimental conditions, but significant amounts of inosine and hypoxanthine appeared in venous effluents during periods of

myocardial hypoxia. Inosine and hypoxanthine are not vasodilators but are rapidly formed from adenosine in heart perfusates or blood. These findings led to the postulation that in hypoxia myocardial nucleotides give rise to adenosine which diffuses out of cardiac cells, induces vasodilatation, but is deaminated and split before separation from the perfusion of blood can be accomplished.

Lemley and Meneely (410) 1952, have demonstrated that anoxia *in vivo* produces alterations in respiratory processes of myocardial tissue as indicated by decreased oxygen consumption of tissue homogenates. These authors demonstrated that the oxygen uptake of homogenized myocardial tissues from rats subjected to anoxia was only one-half that of homogenates from normal animals. Oxygen consumption of homogenized myocardial tissue from anoxic rats could be restored to normal by supplementing with an aqueous extract of boiled hearts from normal rats. It was concluded therefore that the reduced oxygen consumption of myocardial tissue homogenates from animals subjected to oxygen deficiency resulted from loss of inactivation of a heat stable rather than heat labile substance. It was apparently true that the decreased oxygen consumption of anoxic myocardial tissue was not due to destruction of the respiratory enzymes themselves, but rather to a deficit of factors essential for normal activity. Manometric estimation of lactic acid dehydrogenase gave no evidence of any difference in the activity of this enzyme in myocardial tissue of normal rats and those exposed to low oxygen tensions. A moderate reduction in both coenzyme I and cytochrome C was observed in the hearts of rats subjected to anoxia. As to the mechanism by which anoxia damages cardiac tissue, DeHaan and Field (371) 1959, have suggested a hypothesis. It is suggested that lactic acid accumulation resulting from anoxia overcomes the buffer capacity of the sarcoplasm. The consequent increased intracellular acidity results in activation of proteolytic enzymes in the heart tissue and thus to destruction of apoenzyme protein and disruption of metabolic systems. To test this hypothesis and gain information about the well-known resistance of infant tissue to hypoxia, DeHaan and Field subjected adult and infant rat heart muscle to de-

terminations of lactic acid production on anoxic buffer and proteolytic activity. Their results showed that a cathepsin is present in heart tissue which is active only at pH levels below 5 and is almost twice as active in adult heart as in infant heart. Lactic acid accumulates in both infant and adult anoxic hearts, but more rapidly in the adult heart, and in both is accompanied by intracellular proteolysis. The authors suggest that these findings are in accord with the hypothesis.

Two papers concerning EKG changes following breathing of low oxygen mixtures may be cited: Busnengo (362) 1958, found a statistically verified increase in the QT interval in 50 healthy human subjects (average 22.8 years old) and subjected to 9.8 percent oxygen mixtures. Varma and Mellville (441) 1961, induced hypoxia in rabbits by inhalation of 10 percent oxygen and 90 percent nitrogen. Some of the rabbits were normal and the others were maintained on high fat cholesterol diets. During hypoxia greater ST-T depression ensued in the fat-fed animals as compared with the normal, although the duration of hypoxia necessary to produce the effect varied in both groups. In fat-fed rabbits ergometrine maleate induced only slight ST-T depression but when given after 5-10 minutes of hypoxia invariably resulted in marked ST-T depression. This effect appeared in 1-5 minutes and continued under hypoxia (30 minutes maximum) and was readily reversed by placing the animal in room air or in oxygen but was not counteracted by glyceryltrinitrate. The slight ST-T depression produced by the ergometrine alone was readily overcome by similar doses of glyceryltrinitrate. Since hypoxia alone induces coronary dilatation, it seemed likely to the authors that ergometrine enhances myocardial anoxia by producing coronary constriction.

The effect of hypoxia upon the heart rate of the dog, with special reference to the contribution of carotid body chemoreceptors, has been studied by Daly and Scott (367) 1959. The authors' method permitted perfusion of the carotid bodies of anesthetized dogs with blood from the same animal or a donor animal. In spontaneously breathing animals inhalation of seven percent oxygen in nitrogen almost invariably caused an increase in respiratory minute volume and an acceleration of the heart. If during the systemic

hypoxia the carotid body perfusate was changed from hypoxic to oxygenated blood (obtained from a donor dog) further tachycardia occurred together with reduction in the respiratory minute volume. Restoration of hypoxic blood perfusion of the carotid bodies caused a slowing of the heart and the authors therefore concluded that the carotid bodies do not contribute to the production of the tachycardia of systemic hypoxia; on the contrary they antagonize it. Salisbury, Cross and Barron (432) 1963, have concluded that the acute circulatory crisis which supervenes when men or animals are suddenly exposed to arterial oxygen tensions below 45 mm. Hg is not reproducible unless blood having a  $P_{O_2}$  below 45 mm. Hg reaches the common carotid arteries. These studies of cardiovascular effects of hypoxia were carried out on slightly anesthetized dogs by methods which kept that arterial blood pH constant. In some studies isolated hearts were used. Artificial perfusion of the carotid artery, but not of other vascular territories with moderately hypoxic blood, caused a reflex bradycardia with simultaneous constriction of systemic arteries and veins and acute severe heart failure. The authors therefore conclude that hypoxia causes acute circulatory failure through reflex action. Changes of extracranial circulation during hypoxia in young and older healthy men have been studied by Simonson (433) 1960. The author obtained impedance plethysmographic pulse tracings from the forehead before and in the tenth minute after breathing ten percent oxygen, 90 percent nitrogen mixtures. Amplitude and interval changes were compared in 42 young healthy men of 18 to 30 years of age and in 58 older men between 55 and 65 years of age with a drop of arterial oxygen saturation exceeding ten percent. There was no significant change of the peak amplitude and height of the cicrotic notch in the young men during hypoxia, in contrast to a highly significant increase in the older subjects. In both groups there was found a statistically highly significant acceleration of the heart rate and a lengthening of the relative peak time which was more pronounced in the older men. Greater changes of extracranial circulation in the older men during hypoxia, particularly in the amplitudes, may be interpreted as a loss of stability in the peripheral circulation during



stress. For tables on heart rate and respiratory changes associated with reduced  $P_{O_2}$ , the monograph by Van Liere and Stickney (440) 1963, should be consulted. Van Liere, Northup and Baugh (439) 1962, in a study on rats, found that intermittent hypoxia resulted in a relatively greater degree of hypertrophy of the right ventricle than resulted from exercise. The authors suggested that this effect was probably related to pulmonary hypertension known to exist during hypoxic states.

The regulation of cardiac output in hypoxia has been studied in dogs by Gömöri, Kovách, Takács, Földi, Szabó, Nagy, Wiltner and Kállay (393) 1960. In this study cardiac output and total peripheral resistance were measured in 21 dogs maintained on cortisone during hypoxia. Six adrenalectomized dogs were maintained on cortisone and desoxycorticosterone acetate during hypoxia. Twenty-two dogs with isolated cephalic hypoxia, and 6 dogs with isolated hypoxia of the trunk were studied. The studies showed that cardiac output is increased in arterial hypoxia, an increase not influenced by adrenalectomy. Cardiac output increase was induced by hypoxia of the trunk but not that of the head. The authors provide as the most probable explanation that hypoxia gives rise to local vasodilatation. It was not possible to demonstrate the existence of a regulatory mechanism of a neural or endocrine nature.

The effects of hypoxia upon carotid body reflexes have been studied by Neil (423) 1956, and others. Neil has described a technique whereby the carotid bodies can be supplied by carotid blood flow or by oxygenated Ringer-Locke solution from a reservoir. In cats spontaneously breathing five percent oxygen in nitrogen, anoxic tachycardia develops. This tachycardia was not found to be affected if perfusion of Ringer-Locke solution replaces the carotid blood flow through the carotid bodies, although reflex hyperpnea and hypotension result in these conditions. Restoration of the flow of anoxic blood through the carotid bodies after perfusing the glomus tissues with oxygenated Ringer-Locke in cats spontaneously breathing low oxygen mixtures causes hyperpnea, hypertension and subsequent bradycardia. The author considered that

the bradycardia is vagal in origin and appears to be secondary to post-perfusion hyperpnea. It is not seen following perfusion of oxygenated Ringer-Locke artificially ventilated with five percent oxygen in nitrogen mixtures. Neil concludes that the carotid chemoreceptor reflexes make no contribution to the tachycardia of systemic anoxia. According to Neil and Joels (424) 1963, the local tissue tension of oxygen of the glomus cells must represent a balance between the oxygen flow to the tissue and the oxygen usage by the tissue. Therefore if oxygen usage is low in the glomus and oxygen in the blood is low, it may not signal the hypoxia. Systemic hypotension caused by hemorrhage was found to lead to an enormous discharge of chemoreceptor impulses—not even dispelled by administration of pure oxygen in the breathing mixture. Restoration of blood pressure by transfusion abolished the chemoreceptor discharge. It is considered possible by the author that the stagnant anoxia under these circumstances led to an accumulation of metabolites causing excitation of chemosensory endings. The authors stress the fact that the chemoreceptors are particularly responsive to a combination of tissue hypoxia plus hypercapnia and that variations in blood flow through the glomus are of potential importance in modifying the chemoreceptor responses to any gas mixture. The vigorous oxygen usage at the carotid body is masked by the fantastically high blood flow which the glomus ordinarily enjoys. Daly and Scott (368) 1962, have studied the contribution of the carotid baroreceptors and chemoreceptors in maintaining blood pressure during systemic hypoxia. In the anesthetized dog systemic hypoxia usually causes a rise of blood pressure and this response has been attributed to stimulation of chemoreceptors because when the test is repeated after cutting the carotid sinus and aortic nerves, a considerable fall in pressure occurs. However, this procedure also denervated the baroreceptors and this may therefore influence the response. The authors devised a technique for perfusion of the carotid sinuses and bodies which permitted a physiological denervation of the baroreceptors and chemoreceptors independent of each other. Dogs were anesthetized with either a mixture of morphine, chloralose and urethane, or Nembutal, and both vagus

nerves were cut to denervate the aortic arch. With innervated carotid sinuses and bodies, inhalation of 7–12 percent oxygen in nitrogen caused a rise, a small fall or no change in blood pressure. After denervation of the carotid baroreceptors and chemoreceptors hypoxia caused an average fall in pressure of 43 percent. If, however, only the chemoreceptors were denervated, with the carotid sinus baroreceptors remaining innervated, the fall of pressure was less than half this amount. When the baroreceptors were denervated the chemoreceptors being normally functional, systemic hypoxia caused either an increase or a decrease in blood pressure. These results indicated to the authors that the fall in blood pressure in response to systemic hypoxia after division of the sino-aortic nerve is in part the result of denervation of the baroreceptors. Nevertheless the chemoreceptors appear to play an important part in maintaining the blood pressure in hypoxia. In an attempt to quantitate chemoreceptors activity, Hornbein, Griffio and Roos (400) 1961, studied the relationship of chemoreceptor function to acute and chronic hypoxia on the basis of the magnitude of electrical activity of carotid chemoreceptors in response to changes in arterial  $P_{O_2}$  and (+)- $P_{O_2}$ . At a  $P_{aO_2}$  of 40 mm. Hg, changes in blood gas tensions were not reflected in electrical activity of the chemoreceptors. Asphyxia elicited the maximum chemoreceptor response. When respiration was resumed nerve activity dropped to a low level for ten seconds, rose somewhat and then assumed a plateau. This was the transient response. The steady state response was as follows: with ventilation, pH and  $P_{CO_2}$  kept constant, chemoreceptor nerve activity was slight at a  $P_{aO_2}$  of 100 mm. Hg, increased rapidly with decreasing  $P_{aCO_2}$ , and plateaued at a  $P_{aO_2}$  of 30–40 mm. Hg. Extremely low  $P_{aO_2}$  often decreased activity. When (H+)- $P_{CO_2}$  was increased with hypoxia, chemoreceptor activity was potentiated. Chemoreceptor activity in the carotid body of the cat has been explored in isolated preparations by Eyzaguirre and Lewin (384) 1960. Action potentials were recorded from the Hering nerve which had been excised together with the sinus and carotid body and mounted in a flow chamber perfused with 4 ml. per minute Ringer-Locke solution at 37°C., a pH of 7.4 and equilibrated with

varying concentrations of oxygen in nitrogen (from 10–100 percent). The adventitia of the sinus had been removed to eliminate pressoreceptor discharges. Chemoreceptor discharges were present in 100 percent oxygen and increased as oxygen was reduced. With oxygen reduction (50–20 percent) afferent frequency rose to a peak in several seconds followed by a slight decline. With a given  $pO_2$  (e.g. or for example 50 percent) in the perfusion fluid, increases in temperature above 38°C. markedly increased chemoreceptor discharge initially, followed by a decrease. In intact cats under gallamine and controlled ventilation progressive reduction in inhaled oxygen from 100 down to 10 percent increased chemoreceptor frequency. With constant oxygen inhalation of 6 percent carbon dioxide increased chemoreceptor impulses, and small changes in ventilation or blood pressure greatly changed chemoreceptor activity.

A number of papers, now to be discussed, deal with the effects of hypoxia in animals and in man upon pulmonary circulation. Hürliemann and Wiggers (401) 1953, examined the effects of progressive anoxia on the hemodynamic changes in the pulmonary circuit by the rhythmic positive pressure re-breather method on barbitalized dogs with open thoraxes. Calibrated optical manometers of adequate sensitivity and frequency were used for simultaneous recordings of pressures from the aorta, the pulmonary artery and the left atrium. When the air in the spirometer was reduced to ranges of 10–12 percent oxygen, the following changes occurred simultaneously: there was increase in aortic and pulmonary pressure and pulse pressure. Configuration of the pressure pulses indicated augmented stroke volumes of both ventricles and the left atrial pressure was relatively unaffected. Two groups of supplementary experiments in which the blood flow through one entire lung or several lobes was recorded by the electromagnetic flowmeter revealed pulmonary blood flow to be increased concurrently with, but not prior to, elevation of pulmonary and arterial pressure when air mixtures were reduced to 10–12 percent oxygen. Changes in pulmonary arterial resistance, calculated both by using elevated pulmonary pressure and pressure equivalents to control preceeding anoxia, indicated that while some



variation occurs even in the same experiment, resistance is usually increased. The nature and the locus of the resistance and direct or indirect agents operative were not disclosed in the authors' study. Consideration of all the data indicated to the authors that while increase in pulmonary arterial resistance may contribute to rise in pulmonary arterial pressure, increased output of the right ventricle was the major factor. Kuida, Lange, Brown and Hecht (407) 1960, pointed out that the pulmonary vascular response to acute anoxia has been studied in several species with inconsistent results. The occurrence of spontaneous hypertension in calves grazing at high altitude provided a base for specifically examining the response in the bovine species. Using cardiac catheterization, dye dilution techniques and endotracheal intubation, measurements were made of pulmonary and carotid arterial pressures and oxygen saturation, as well as cardiac index, and calculated pulmonary vascular resistance before and after exposure to gas mixtures of 10–16 percent oxygen in air for 5–20 minutes. Sixteen anoxic periods were produced in 13 unanesthetized normal calves with a fall in oxygen saturation from control levels of 87–91 percent, averaging 33 percent  $\pm$  18. Four animals developed saturations less than 50 percent of the controls. Pulmonary arterial pressure increased in 14 of 15 instances, averaging 12 mm. Hg or  $\pm$  52 of controls. Cardiac index rose in eight and fell in three animals; the average change being +13 percent  $\pm$  23. Pulmonary vascular resistance increased in ten and remained unchanged in two, with an average percentage increase over control data of +65 percent  $\pm$  77. This study indicates that in calves acute anoxia is generally associated with an increase in pulmonary vascular tone. By means of chronically implanted vinyl catheters Thilenius, Hoffer and Fitzgerald (437) 1961, recorded pressures in the aorta, the pulmonary artery and the left atrium, as well as the intrapleural space (by capsule), together with cardiac output by dye dilution technique every two minutes. These studies were carried out in unanesthetized, unsedated, trained dogs for one hour during breathing of air and low oxygen mixtures (6–10 percent) via chronic tracheostomy.

In nearly all of 35 experiments on six animals there were striking responses to hypoxia, consisting of a marked rise in pulmonary arterial pressure (up to 100 percent) in cardiac output (up to 80 percent) in pulmonary vascular resistance (up to 200 percent) and of a significant fall in left atrial pressure (up to 75 percent). These changes were not maintained throughout hypoxia. The pulmonary ventricular resistance usually returned towards normal first, followed by pulmonary arterial pressure, the cardiac output usually remaining elevated. The time sequence of these events varied in different animals. Effects of the same magnitude, as in hypoxia, accompanied restlessness caused by stress, but fluctuated markedly, were of shorter duration, and could largely be eliminated by providing quiet surroundings and by avoiding prolonged experiments. The dilating action of anoxia on pulmonary vessels has been examined by Aviado, Cerletti, Alanis, Bulle and Schmidt (385) 1952. Dogs under morphine and chloralose, subjected to spontaneous inhalation of 5 or 10 percent oxygen responded as follows: the pressure of the cannulated lobar artery increased by about 30 mm. of H<sub>2</sub>O with an arterial blood saturation of 60 percent. This pulmonary hypertension was caused chiefly by an anoxic rise in pulmonary flow. When the flow to the lung on one side was kept constant by pumping the mixed venous blood from the right auricle to the pulmonary artery, the corresponding pulmonary arterial pressure decreased while the pressure of the other side supplied by its own heart increased during anoxia. An isolated perfused lung showed vasodilatation when the oxygen content of either the ventilating air or the perfusing blood was reduced. The observed pulmonary hypertension in anoxic intact dogs was the combination of this local vasodilatation and of the increased pulmonary flow. The latter was elicited by the anoxic stimulation of carotid and aortic chemoreceptors and by the liberation of epinephrine. The net result of these responses was reflected in the radioactive measurement of erythrocytes tagged with P<sup>32</sup> by means of a beta counter applied to the surface of the lung. This estimation of capillary blood volume in the lungs was observed to increase by about 10 percent during anoxia. All of these results in dogs were



found to be different from the reports that low oxygen content constricts the perfused pulmonary vessels of cats. Aviado, Cerletti, Alanis, Bulle and Schmidt (354) 1952, also commented on the rise in pulmonary arterial pressure observed in anesthetized dogs inhaling 5–10 percent oxygen and explained this by increased pulmonary flow through carotid and aortic chemoreflexes and epinephrine liberation. A total dilation is seen when the innervated lung is perfused with blood of low oxygen saturation or when ventilated with low oxygen mixtures. In the dog estimations of the volume of the blood in the lungs (by  $P^{32}$ ) in animals breathing spontaneously indicated that there was an increased amount of blood during anoxia. There was no evidence of any constrictor action of anoxia on the pulmonary vessels in this species. Gorlin and Lewis (394) 1952, and Lewis and Gorlin (411) 1952 have reported on the effects of graded hypoxemia on the pulmonary circulation of the dog. In their studies of severe hypoxemia they used dogs anesthetized with morphine-chloralose-urethane and subjected them to breathing mixtures containing 2.5–10 percent oxygen on several occasions. Arterial oxygen saturation varied from 8–55 percent depending upon the inspired oxygen percentage. The mean pulmonary arterial and left atrial pressures were measured with indwelling catheters via the jugular vein and femoral artery respectively. Integrated cardiac output was measured by the Fick principle, using the Benedict-Roth method for oxygen consumption. Pulmonary vascular resistance was calculated. Observations were made at intervals varying from 3.5 minutes to 8 hours after induction of hypoxia. When the arterial oxygen saturation was above 15 and less than 55 percent, the cardiac output increased from 40 to 300 percent above control values. Oxygen consumption remained unchanged. Mean pulmonary arterial pressure rose moderately while left arterial pressure remained the same or decreased. Pulmonary vascular resistance remained unchanged or actually decreased, regardless of the time duration of hypoxia. When arterial saturation was less than 15 percent left atrial pressure rose. In some observations cardiac output increased and in others remained the same or decreased. Pulmonary arterial pressure increased uniformly. No changes in pulmo-

nary vascular resistance were observed. In these experiments arterial saturation was so low that tissue oxygen demands could be met only by increase in blood flow. Under these circumstances, although there was a wide variation in the degree and duration of the severe hypoxemia and in the cardiac response to hypoxemia, no alterations in pulmonary vascular resistance were demonstrable. Under conditions of moderate hypoxemia the authors studied dogs anesthetized also with morphine-chloralose-urethane anesthesia. These animals were subjected to breathing mixtures containing 10 percent oxygen. The duration of hypoxia varied from 20 minutes to 8 hours during which several sets of observations were made. Arterial oxygen saturation varied from 55–79 percent. Pulmonary arterial and left atrial pressures were recorded through indwelling catheters and the cardiac output was also measured by the Fick principle. Pulmonary vascular resistance was calculated from the Poiseuille equation. The cardiac output did not vary significantly from control values regardless of the duration of hypoxemia. Oxygen consumption and arterio-venous oxygen differences did not change appreciably. Pulmonary arterial pressure rose somewhat and left atrial pressure fell so that the pulmonary pressure gradient increased. Pulmonary vascular resistance showed a statistically significant increase. The degree of increase varied directly with the duration of hypoxemia. A dog exposed to hypoxia for seven hours with a rise in pulmonary vascular resistance was then allowed to breathe room air for three hours and subsequent observations showed a fall in pulmonary vascular resistance. When the hypoxia is mild the authors' experiments are similar to those of others who have observed pulmonary vasoconstriction, however, previous experiments of this group of authors have shown that when hypoxia is so severe that cardiac output must rise to maintain tissue oxygen supply, the pulmonary vascular resistance does not rise. The former may be due to a local effect of hypoxia on the lungs, while hypoxia of the body as a whole appears to reverse the pulmonary vasoconstriction. Lewis, Gorlin and Houssay (412) 1953, found that moderate hypoxia produces an increase of pulmonary vascular resistance with an unchanged cardiac output. Since this occurs in the isolated perfused lung

and with unilateral as well as bilateral hypoxia, it seems to be due to the local action of low oxygen tensions. Severe hypoxia produced three types of response in spontaneously breathing dogs that hyperventilated during hypoxia: a) maintained oxygen consumption, increased cardiac output, unchanged left atrial pressure and unchanged pulmonary vascular resistance; b) maintained oxygen consumption, increased cardiac output and left atrial pressure and unchanged pulmonary vascular resistance; c) decreased oxygen consumption and cardiac output, increased left atrial pressure and unchanged or increased pulmonary vascular resistance. The influence of hyperventilation was investigated in a number of dogs with open chests, ventilated at a constant volume by a Starling "Ideal" pump. The pressure gradient was measured from pulmonary arterial and left atrial catheters. Fick cardiac outputs were determined. During severe hypoxia, produced by breathing 5 percent oxygen, the oxygen consumption fell lower than in those with spontaneous respiration, but three types of circulatory responses were again seen: a) increased cardiac output, unchanged left atrial pressure and pulmonary vascular resistance; b) increased cardiac output and left atrial pressure, with unchanged pulmonary vascular resistance; c) decreased cardiac output, increased left atrial pressure, and a tendency to increased pulmonary vascular resistance in several experiments and a distinct rise in one experiment. This indicated to the authors that ventilation *per se* had no influence on the pattern of response at any given level of arterial oxygen saturation, including the pulmonary vascular resistance.

The pulmonary effects of moderate and severe hypoxia in the dog were examined by Stroud and Conn (436) 1954. In these experiments pentobarbital anesthetized dogs were used in a redetermination of the effects of hypoxia on the pulmonary vascular bed using a radioactive isotope dilution technique for measuring cardiac output instead of the Fick procedure. Experiments were divided into a control period, followed by 5–12 minutes during which 10 percent oxygen was breathed by the dogs, a 5–12 minute recovery period, and a 5–12 minute period with 5 percent oxygen. With 10 percent oxygen (arterial oxygen saturation of 79 percent) a small

mean increase in cardiac output was accompanied by significant increase in pulmonary arterial pressure and resistance. With 5 percent oxygen (arterial oxygen saturation of 46 percent) there was a small increment in cardiac output with a small additional rise in pulmonary pressure and resistance. These "small rises" are probably not at all significant according to the authors. In all dogs there was a small average increase in systemic arterial pressure with no change in systemic resistance. In addition to expected ventilatory responses, there were significant increases in circulation time and 'pulmonary' blood volume. No arterial-venous shunting was evident from the isotope dilution curves which should reveal a bypass of 4 percent or more of the cardiac output. Nahas (421) 1956, conducted a study, the purpose of which was to investigate the influence of moderate hypoxia on the pulmonary circulation, in dogs after eliminating the ventilatory response to hypoxia and its secondary effects on circulation. After pentothal anesthesia, dogs were fitted with catheters in the pulmonary artery and vein, the right atrium and the descending aorta. Respiratory arrest was induced by curare-like compounds and mechanical breathing instituted. Photokymographic records of pressures and cardiac output determinations were made during artificial respiration and at the end of 90-second periods of 'apneic oxygenation' and 'apneic hypoxia'. 'Apneic oxygenation' was considered to be a period of respiratory arrest following denitrogenation of the animal and during which the trachea is connected to a reservoir containing 100 percent oxygen. 'Apneic hypoxia' was defined as a period of respiratory arrest following ventilation with room air. After 90 seconds of 'apneic oxygenation' mean pulmonary arterial and venous pressure and the pressure gradient between the pulmonary artery and the vein were significantly lowered. The mean femoral artery pressure was significantly increased. Cardiac output and calculated pulmonary and peripheral resistance were not changed. During 'apneic hypoxia' (with arterial oxygen saturation in the vicinity of 50 percent) mean pulmonary arterial, pulmonary venous, femoral arterial pressure and pressure gradient between the pulmonary artery and vein were significantly increased. Calculated



pulmonary and peripheral resistance rose significantly from 2.5 to 3.6 and from 45 to 54 mm. Hg respectively. These increases occurred in the presence of a significant fall in heart rate and in right atrial pressure, while cardiac output did not change significantly. Duke (378) 1954, found that inhalation of gas mixtures containing 5–10 percent oxygen in nitrogen in cats caused a rise of left pulmonary arterial pressure in the living animal during perfusion of the left lung at constant volume inflow with blood from the right auricle. This response was not found to be dependent on changes in left auricular pressure, tidal air or systemic blood pressure. It was similar in duration and latency to that occurring in isolated lungs perfused at constant volume inflow. Perfusion of isolated lungs with partially deoxygenated blood did not cause a rise of pulmonary arterial pressure if the lungs were respiring air. Ventilation of the lungs with nitrogen during perfusion with partially deoxygenated blood did cause a rise of pulmonary arterial pressure. Inhalation of nitrogen by isolated perfused lungs caused a similar rise of inflow pressure, whether perfusion was made through the pulmonary artery or through the left auricle. Duke (379) 1957, found in isolated cats' lungs perfused through the pulmonary artery with the animal's own heparinized blood at constant volume inflow, that ventilation of the lungs with nitrogen instead of air produces a rise in pulmonary arterial pressure and a fall of left auricular pressure. The pressor responses to nitrogen occurred in preparations made from animals in which the lungs were chronically denervated. There was no evidence of a circulating vasoconstrictor substance on perfusing the cat's denervated hind limb with blood which has been partially deoxygenated in the lungs. Pulmonary pressor responses to hypoxia were found in isolated perfused dogs' lungs and in anesthetized dogs with left lung perfusion. In the anesthetized cat with left lung perfusion the increase of left pulmonary arterial pressure in response to inhalation of 5 percent oxygen in nitrogen was not prevented by removal of both adrenal glands. In normal human subjects, Goldring, Turino, Cohen, Jameson and Fishman (392) 1960, measured the concentrations of epinephrine and norepinephrine in the arterial and mixed venous

blood during three experimental circumstances: 1) breathing of 11 percent oxygen (acute hypoxia); 2) the infusion of norepinephrine; and 3) hypoxia plus infusion of norepinephrine. The measurements included cardiac output (by the direct Fick method), central blood volume (by dye dilution), and blood pressures (pulmonary and brachial artery as well as pulmonary wedge pressures). Results indicated: 1) the absence of abnormally high quantities of epinephrine or norepinephrine during acute hypoxia; 2) the need for a ten-fold increase in circulating epinephrine or norepinephrine to duplicate the pulmonary arterial hypertension of acute hypoxia; and 3) unchanged wedge pressures during hypoxia and increased wedge pressures during norepinephrine infusion. In other subjects injection of norepinephrine into the pulmonary artery during open thoracotomy showed that a rise in left atrial pressure anteceded the rise in pulmonary arterial pressure. The pulmonary pressor response to acute hypoxia in man was not found to be related to circulating levels of epinephrine and norepinephrine. Bergofsky, Lehr, Tuller, Rigatto and Fishman (357) 1961, found that neither intravenous injection of 0.4 molar sodium bicarbonate nor 0.3 molar tris-hydroxymethylaminomethane (300 ml. over 25 minutes) modified the pulmonary arterial pressor response to hypoxia in man (12 percent oxygen) indicating that neither extracellular or intracellular acidosis appeared to play a role in the pressor response. In anesthetized dogs breathing 5 percent oxygen and infused with lactic acid or hydrochloric acid, there was a consistent rise in pulmonary arterial pressure during acute acidosis with no change in pulmonary blood flow or left ventricular blood pressure, suggesting pulmonary vasoconstriction. Increased pulmonary vascular resistance in relation to decreased blood pH was the same regardless of the method used to induce the acidosis, suggesting that the hydrogen ion rather than the associated anion is responsible for the pulmonary vascular response. In human subjects, Bishop, Harris and Segal (359) 1961, found that hypoxia caused a rise in pulmonary arterial pressure and an increase in cardiac output with no change in pulmonary wedge pressure. After producing postganglionic sympathetic blockade with guanethidine (10–27 mg. intraven-



ously) hypoxia caused a greater average rise in pulmonary arterial pressure and a lesser increase in cardiac output and no change in pulmonary wedge pressure. These findings suggested to the authors that the effects of hypoxia on human pulmonary circulation are not mediated by the sympathetic nerves since the differences before and after post-ganglionic sympathetic blockade were slight. The experiments suggested that the sympathetic system plays no substantial role in governing the normal tone of the pulmonary vessels at rest.

Peters and Roos (426) 1952, have investigated the effect of unilateral nitrogen breathing upon pulmonary blood flow in the dog. Blood flow through each lung was determined by the Fick principle both during bilateral oxygen breathing and during unilateral nitrogen breathing, the other lung receiving oxygen. Vascular resistance of each lung was calculated from mean pulmonary arterial pressure and blood flow. In all but a few animals there occurred a reduction of 16–68 percent of the original fraction of total flow to the nitrogen lung. The maximal effect was already present after 25 minutes, and was promptly reversible on return to bilateral oxygen breathing. Resistance in the nitrogen lung was increased by factors of 1.3 to 4.5 while in the oxygen lung it remained essentially unchanged. Lanari-Zubiaur (408) 1957, and Lanari-Zubiaur and Hamilton (409) 1958, also in experiments on the dog, found no consistent flow change in the anoxic lung and concluded that the physiologic consequence of increased pulmonary resistance to flow due to anoxic breathing is of doubtful meaning in the dog. In human subjects, Himmelstein, Harris, Fritts and Cournand (399) 1958, administered 5 percent oxygen to one lung and found that there was a reduction in the fraction of total flow perfusing the hypoxic lung in 3 of 5 normal subjects. In the fourth the results were inconclusive, and in the fifth subject pulmonary hyperventilation developed with no change in the partition of flow. Fishman, Himmelstein and Cournand (387) 1955, found that a sharp reduction in the oxygen content of inspired gas elicited pulmonary hypertension in man. In an attempt to analyze further the mechanisms underlying this pressor response they confined the hypoxic stimulus (8–12 percent

oxygen) to one lung, while the other lung breathed a gas mixture enriched with 25–33 percent oxygen. The blood flow was measured by the Fick principle through both lungs as well as through the hyperoxic one. Flow through the hypoxic lung was obtained by difference. In seven subjects in whom the arterial blood oxyhemoglobin during unilateral hypoxia did not fall below 85 percent, the total minute ventilation and gas exchange for both lungs remained unchanged. During this period, regardless of whether total blood flow stayed the same or increased slightly, the proportion of blood flow through each lung was unaltered. Since in these experiments the hypoxic stimulus was unilaterally applied to one lung and to its post-arteriolar vascular bed, failure to demonstrate any shift of blood from the hypoxic lung suggested that these pulmonary segments do not participate in the pressor response to acute hypoxia. In 1955 Cournand (364) concluded that the most likely cause of the increase in pulmonary arterial pressure, observed while breathing the hypoxic inspiratory mixture in man, was the association of an increased pulmonary blood flow together with some other hemodynamic factor related to severe arterial hypoxemia (probably displacement of blood from the systemic to the pulmonary vascular bed).

Doyle, Wilson and Warren (377) 1952, have shown differences in pulmonary vascular responses to short term hypoxia in normal subjects and those with various cardiopulmonary abnormalities. The normal group with oxygen saturation about 75 percent showed considerable increase in pulmonary vascular resistance. The abnormal group with similar oxygen saturation showed smaller increases in pulmonary vascular resistance and little or no change in cardiac output. Pulmonary capillary pressure was unaltered in both groups. In contrast to the normal group, low oxygen caused severe dyspnea in the abnormal group. There was no evidence of alterations of pulmonary blood volume during hypoxia in either group. Fritts, Harris, Clauss, Odell and Cournand (391) 1958, infused acetylcholine into the pulmonary artery of normal human subjects under normal and hypoxic conditions. This drug caused a fall in pulmonary arterial pressure which was more evident after hypoxia had pro-

duced pulmonary hypertension. The fall in pressure was not associated with a fall in cardiac output and there was no change in the pulmonary wedge pressure, heart rate, systemic blood pressure or central blood volume. It was concluded that acetylcholine causes pulmonary vasodilatation. Apparently the effect is enhanced in the presence of an increased vascular tone.

The effect of hypoxia upon blood flow in various areas has been studied experimentally by a number of investigators. Rota and Rossanigo (430) 1958, found that in human subjects exposed to 7.7 percent oxygen there was an increase in flow index (average increase of 33 percent) as measured by rheographic recordings from the wrist and calf. Fairchild, Crawford and Guyton (385) 1959, studied the relation of blood flow through the hind limb of a dog to the gaseous content of the blood. In one series of dogs the oxygen saturation of the blood flowing through the leg was gradually changed by adding various amounts of venous blood to arterial blood. As the oxygen saturation decreased, the blood flow increased, slowly at first and then progressively more rapidly as the oxygen levels fell lower and lower. Even though the oxygen saturation in most experiments was decreased to 30 percent, the total oxygen transported to the tissues each minute decreased only to 75 percent of the control value, showing that a definite compensatory mechanism exists with an efficiency of about 65 percent, for preventing tissue hypoxemia. In another group of animals the oxygen saturation of the blood was maintained constant while the dogs were allowed to breathe 20 percent carbon dioxide for an hour. By checking the blood flow every 10 minutes it was found that there was no increase in blood flow, but rather in three of the animals a decrease to the extent of 35 percent of the control blood flow, and in the remaining two no change. These studies indicate that oxygen deficiency might well be one of the causes of reactive hyperemia but that excess carbon dioxide is probably not involved.

As Carrier and Guyton (363) 1963, have pointed out, one of the most perplexing problems in the circulation field has been the mechanism by which blood flow is regulated in response to tissue metabolic needs. One thesis that has been advanced is that low oxygen levels in the tissues

cause the arterioles to dilate, thus allowing more flow and a consequent increased nutritive supply to the area. To investigate this problem, the authors took isolated segments of very small arteries, 0.5–1.0 mm. in diameter and 1.0 cm. in length, from the dog and using various perfusion techniques found a direct correlation between oxygen level in the perfusion blood and resistance. For example, in a series of six vessels perfused under constant pressure of 100 mm. Hg, they obtained a graded response to stepwise increase of  $pO_2$  from 30 mm. Hg to 100 mm. Hg. In this series the individual vessels gave up to 143.0 percent increase in resistance, the average response being 72.9 percent. Changes in resistance of this magnitude can maintain the supply of oxygen to a tissue very nearly constant despite striking changes in oxygen supply. The authors therefore concluded that tissue oxygen pressure may well be the major stimulus for local autoregulation of blood flow in response to an area's needs. Comparable results have been reported by Black and Roddie (360) 1958, in normal human subjects who breathed 5–10 percent oxygen in nitrogen for 2–6 minutes. Forearm blood flow, as measured by venous occlusion plethysmography, was increased along with ventilation and heart rate. Studies by McGiff and Aviado (416) 1961, in dogs subjected to hypoxia (5 percent oxygen) indicate that the femoral bed's resistance is reduced significantly more than the reduction in renal vascular resistance. These results suggest that the femoral bed is more reactive than the renal following baroreceptor or chemoreceptor induced changes. In contrast, the renal bed appeared to be more susceptible to hormonal stimuli. Hypoxia caused a greater increase in femoral resistance than in renal resistance.

Dil, Litwin and Aviado (375) 1960, showed that vasoconstriction in the hind limb of the anesthetized dog occurred during inhalation of 5 percent oxygen while vasodilatation occurred during reoxygenation. Both of the responses were eliminated by a transection of the cervical spinal cord. Denervation of chemoreceptors or combined adrenalectomy and blockade of sympathetic nerves by bretylium reduced the vasoconstrictor but not the vasodilator response. The responsible vasodilator nerves are partially



blocked by either hexamethonium or atropine, but are resistant to sympathetic blocking drugs. Human subjects breathing air, 11.5 and 7.5 percent oxygen in nitrogen, were shown by Eckstein and Horsley (383) 1960, to have insignificant changes in venous tone with 11.5 percent oxygen, but active venous constriction with the 7.5 percent oxygen mixture. This constriction was sufficient to displace small amounts of blood from the extremity. The change in venous tone could not be attributed to mild hyperventilation which occurred with low oxygen breathing.

The influence of acute hypoxia on peripheral and central venous pressures have been studied by Nahas and Josse (422) 1954, in the non-narcotized dog trained to breathe 8 percent oxygen in nitrogen. Two series of experiments were carried out. In the first, pressures were measured in superior and inferior vena cavae through cardiac catheters. In addition intrathoracic pressure was simultaneously recorded through an intrapleural cannula. In the second series of experiments, small vein and veinule pressures were measured in the dog's foreleg. In both series, control measurements were recorded at one minute intervals with the animal breathing room air. After that control period the animal was switched to the lower oxygen mixture for ten minutes and measurements were taken at one minute intervals. The animal was then returned to room air and similar measurements taken during the recovery period at one minute intervals. Vena caval pressures were corrected with reference to the simultaneously recorded intrapleural pressures. During exposure to 8 percent oxygen there was no change in the effective pressures in the superior or inferior vena cavae. Under similar conditions there was a 2.3 mm. Hg and a 1.4 mm. Hg increase in the veinule and small vein pressure respectively in the dog's forelegs. The pressure gradient between the veinule and vein was similarly observed to rise during hypoxia.

At critical levels of hypoxemia there is edema formation in perfused rat hind limbs. Di Pasquale and Schiller (376) 1951, found in hind limbs perfused with blood of low colloidal content that 5.5–9.4 volumes percent oxygen content of the perfusate were adequate in maintaining capillary function with a minimum rate of edema

formation not varying appreciably with flow. Hind limbs perfused with 0.88–2.60 volumes percent oxygen exhibited augmented edema formation which increased with increased flow. The critical hypoxemia level affecting capillary permeability is believed to lie between 2.6 and 5.5 volumes percent oxygen content. Hendley and Schiller (398) 1954, perfused isolated rat hind legs with buffered Krebs-Ringer solution containing washed red cells and 0.33 percent gelatin. Edema formation with mild hypoxia (5–10 percent oxygen content) was slight, but with severe hypoxia (0–5 volumes percent) an elevated rate of edema formation in excess of predicted formation from associated hemodynamic changes indicated increased capillary permeability. Distribution of perfused intravascular colloidal dye suggested decreased vascular resistance and increased permeability of capillaries to colloidal particles occurring in skeletal muscle vasculature during severe hypoxemia.

For clinical reports of the action of hypoxia and recommendations for treatment, papers by Miles (419) 1957, and Francheteau (389) 1954, should be consulted.

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## 5. BLOOD

It is well known that conditions of hypoxia, if severe enough, serve as a stimulus for erythro-

poiesis. Short exposures may have no effect as demonstrated by Pannacciulli, Fumagalli and Mezzano (459) 1958. In studies of normal students, they observed that hypoxia (8.6-11.2 percent oxygen) at sea level for five minutes caused no immediate blood changes. There was sometimes a moderate inconsistent reticulocytosis. Lambersten, Bunce, Drabkin and Schmidt (457) 1952 examined the relationship of oxygen tension to hemoglobin oxygen saturation in the arterial blood of normal men. In their experiments the relationship of percentage hemoglobin saturation  $pO_2$ ,  $pCO_2$  and pH were determined in normal subjects by analysis of arterial blood collected during inhalation of gas mixtures from 21-4 percent oxygen in nitrogen. The percent oxygen saturation was measured by both spectrophotometric and manometric methods in an attempt to evaluate apparent discrepancies between results obtained by previous investigators using one or the other technique. No difference in dissociation characteristics of oxyhemoglobin were detected in the subjects tested. Simultaneous measurements of percent oxygen saturation and  $pO_2$  indicated closer agreement with *in vitro* dissociation curves of other workers.

It is well known that infants have hemoglobin with a higher affinity for oxygen than that of the adult, and that hypoxia tolerances are greater in proportion to affinity. Barker (448) 1956 reported modifications of hemoglobin affinity and hypoxia tolerance in infant and adult rats following exposure to low and high oxygen tension. High affinity hemoglobins with high tolerances were found in some adult rats and mice after exposure to low  $pO_2$ . Further studies indicated that high affinity hemoglobin appeared within 24-72 hours in all adult rats exposed for two hours daily to a  $pO_2$  of 50 mm. Hg, affinities often exceeding the mean for newborn rats if exposures were continued for a week. Exposures to a  $pO_2$  of 27 mm. of Hg for 10 minutes, or of 90 mm. of Hg for 20 hours, were less effective. Polycythemia does not necessarily accompany the shift. If high affinity hemoglobin, which normally occurs only in infants, is a consequence of intrauterine hypoxia, its production might be inhibited by high  $pO_2$ . In newborn rats exposed to 50 percent oxygen for 72-96 hours, the disappearance of high affinity hemoglobin and of hypoxia toler-



ance was greatly accelerated, and the infants were more anemic than controls. Although affinities did not increase on removal to air, they did on exposure to low  $pO_2$ . Since no high affinity hemoglobin was found during recovery from severe hemorrhage, its appearance was considered probably not related to a specific phase of erythrocyte development. Splenectomized rats readily produce high affinity hemoglobin on exposure to low  $pO_2$ . No abnormalities attributable to the presence of high affinity hemoglobin were observed. In 1960, Kalff (455) determined hemoglobin values and erythrocyte counts in a group of 50 pilots before and during exposure to hypoxia in a low-pressure chamber. A significant increase in the erythrocyte count and hemoglobin values over the initial values was noted in all subjects after three minutes exposure to anoxia. Measurements taken in the sixth minute showed a significant drop of these values from the initial level. A third measurement taken during the ninth minute of exposure to anoxia showed a tendency towards a slight increase in the hemoglobin and erythrocyte values. Some individuals showed more labile erythrocyte and hemoglobin values with wider fluctuation ranges than did others.

For a consideration of hypoxia as a stimulus for erythropoiesis, papers by Grant and Root (453) 1952, and Root (461) 1954, should be consulted. Hypoxia is one of the commonest conditions associated with erythropoiesis and one of the most convenient means of experimentally producing erythroid stimulation. However, hypoxia does not act directly on the bone marrow according to Grant and Root. These authors consider that there is no convincing evidence that erythropoiesis is controlled directly by the nervous system or by hormones of any single endocrine gland. Presumably lack of oxygen at some unknown region in the organism activates processes which release an erythroid stimulating agent.

Effects of hypoxia on leucocyte formation have been studied by Altschul, MacFayden and Whitehead (447) 1957. In these authors' experiments mice of the leukemia strain, AKR (Jax), were exposed to prenatal hypoxia by subjecting the mothers to a single period of five hours at atmospheric pressure with oxygen percentages equivalent to conditions of 25,000 feet above sea level. This exposure was usually carried out dur-

ing the 8–14 days of gestation. The offspring were studied for the appearance of leukemia. The offspring which had been subjected to this prenatal hypoxia revealed inhibition of leucocytosis. This inhibition was more pronounced and highly significant in males, but was not significant in females. It was concluded that prenatal hypoxia was the responsible factor in the inhibition in the males. Hypoxia experienced during the seventh to tenth days of gestation was more effective than that undergone later, but the difference was not highly significant.

A number of reports on the effects of hypoxia on plasma may now be considered. Battaglia, Meschia, Hellegers and Barron (449) 1958 found in experiments on adult rabbits, sheep, goats, lambs, and fetal sheep and goats that the osmotic pressure of the plasma invariably rose as a consequence of acute severe hypoxia. The findings of the authors were interpreted as suggesting that severe acute hypoxia causes a rise in intracellular osmotic pressure as a manifestation of a shift from aerobic to anaerobic metabolism. Intracellular rise in osmotic pressure would result in movement of water out of extracellular fluids and thus increase their effective electrolyte concentration. Transcapillary passage of plasma proteins may occur in hypoxia, but Schiller and Wool (462) 1952 showed in intact rats that grades of hypoxemia corresponding to a  $pO_2$  of 25 mm. Hg or an oxyhemoglobin saturation of 30 percent do not produce hemodynamic or permeability changes which significantly alter transcapillary passage of plasma proteins. The concentration of H ions, carbonic acid and bicarbonate in the blood and blood plasma before and during and after acute hypoxia has been measured by Kunamann (456) 1960 in human subjects. Hypoxic hyperventilation after five to six minutes at an atmospheric pressure of 287 mm. Hg was observed to produce a decrease in  $pCO_2$ , an increase in bicarbonate concentration and an increase in the pH of the blood. During extended hypoxia the bicarbonate concentration and pH were decreased by the compensatory reaction of the kidneys in excreting bicarbonate ions while retaining hydrogen ions. Full recovery of the blood electrolyte balance was still incomplete one hour after return to normal atmospheric pressure.

Recently heparin has been recommended as an adjunctive agent in recompression treatment and as a prophylactic agent in decompression sickness as well as a drug in the specific treatment of decompression sickness. Its efficacy for these purposes is still under debate and the mechanism of action has not been delineated. For this reason the effects of heparin on the actions of acute hypoxia on blood chemistry are of interest. Otey (458) 1953 points out that the anticoagulant effect of heparin has been thoroughly investigated, but with the exception of its lipid clearing effect, little work has been done on its possible metabolic functions. Otey's study was carried out to see what effect heparin may have on metabolism during hypoxia. In his studies anesthetized dogs were given heparin in doses of 5-10 mg./Kg. body weight. Following a control period of breathing room air, arterial oxygen tension was reduced to about 40 mm. Hg and held at this level for about two hours. Arterial blood samples were taken at ten minute intervals for analyses. Lactate and pyruvate concentrations did not change significantly from control values throughout the duration of the hypoxia. In a control group of animals receiving no heparin lactate and pyruvate both rose initially with pyruvate leveling off while lactate continued to rise. In a group of heparinized animals, protamine sulfate was given to antagonize the heparin while the hypoxia continued. In these animals, which had shown no increase in lactate or pyruvate prior to the administration of protamine, now showed the expected increase in lactate. Otey concluded from these experiments that heparin prevents either the production or release of lactate during hypoxia.

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## 6. CEREBROSPINAL FLUID

Leusen and Demeester (466) 1960 have reported changes in the cerebrospinal fluid in dogs subjected to breathing ten percent oxygen at ambient pressure. The pH of the cerebrospinal fluid paralleled the changes in blood pH during



hypoxia and increased ventilation was also recorded. The arterial pH under hypoxia was 7.49, cerebrospinal fluid pH was 7.44, the bicarbonate in plasma 19.5, cerebrospinal fluid bicarbonate 23.0,  $PCO_2$  in blood 23, and in cerebrospinal fluid 35.

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## 7. RESPIRATION

In this section there has been included in the reference list a number of papers dealing with the complexities of respiratory physiology under conditions of hypoxia. Only a fraction of these are discussed in the text that follows. Respiratory patterns of divers subjected to hypoxia and carbon dioxide have been studied by Miles (483) 1957. In this report Miles conducted a survey of 100 divers which indicated that a very wide variation existed in respiratory responses when the divers were exposed to identical conditions. The subjects breathed from a balanced spirometer filled with air and a carbon dioxide absorbent. The air mixture breathed in these studies contained 10-11 percent oxygen. In general, no changes were seen in the first five minutes, but in the subsequent four or five minutes hypoxic effects began to appear. After a period of rest the procedure was repeated, except that carbon dioxide was allowed to accumulate (to levels of five or six percent). In a third and final series 100 percent oxygen was used, but again carbon dioxide was allowed to accumulate. Breathing normal air the minute volume ranged from 7.6 to 33.2 liters, with rates from 6-32 per minute. The tidal volume varied from 442 to 3259 cc. The responses were not considered extreme but were either slow and shallow or fast and deep. Thirty-two of the 100 subjects had somewhat irregular patterns, characteristically free of any rhythm. Periodic inspiratory spikes were seen in shallow breathers. In the first series (effects of hypoxia alone) 58 patients showed elevated minute volume, 39 a depressed minute volume, and three no change. Of the 39 showing a reduction, 31 had a reduced tidal volume and nine a reduced rate, while nine showed no rate change at all. Thirteen revealed an elevation of rate. The remaining eight showed a reduction in rate

along with the change in tidal volume. The variations in tidal volume were more significant than the rate variations. For the series in which carbon dioxide was allowed to accumulate with 100 percent oxygen, three men showed a reduction in ventilation and 15 an increase in their minute volume over 150 percent. When carbon dioxide was allowed to accumulate in air, as opposed to 100 percent oxygen, there was an increase in minute volume from 0 to 150 percent. In oxygen, a greater proportion fell in the lower ranges of increase. The slow-deep breathers responded less to carbon dioxide than the fast and shallow ones. The authors suggest that shallow breathers might be less efficient when using apparatus which introduced additional dead space. Shallow breathers probably retain more carbon dioxide. The shallow-fast breathers may have difficulty with increased dead space and increased resistance or increased gas density. The slow-deep breathers are probably the best subjects and are the best divers in this group. The hyperventilators are less acceptable as divers, adding to the hazards of diving. Lambersten, Wendel, Chiodi and Owen (486), 1957, have examined the respiratory effects of .08 and .8 atmospheres of inspired  $P_{O_2}$  at "constant" alveolar  $P_{CO_2}$  of 43 mm Hg. In these studies 8, 21 and 80 percent oxygen were administered at one atmosphere to six normal subjects maintained at an alveolar  $P_{CO_2}$  of 43 mm Hg. In the absence of alterations in arterial  $P_{CO_2}$  or pH, 8 percent oxygen produced a 26 percent increase, and 80 percent oxygen resulted in a 15 percent increase in respiratory minute volume above the control values obtained during 21 percent oxygen breathing. The respiratory stimulation associated with 80 percent oxygen breathing was accompanied by a significant 1.6 mm Hg rise in cerebral venous  $P_{CO_2}$ , reflecting a central hypercapnia which may have produced the "oxygen" hyperpnea. Since neither cerebral circulation nor cerebral metabolism was altered by 80 percent oxygen, the internal jugular venous hypercapnia was due to diminished hemoglobin reduction. The hypoxic hyperventilation of eight percent oxygen breathing was associated with a five mm Hg fall in cerebral venous  $P_{CO_2}$ , due to increased rate of brain blood flow. It was therefore considered possible that, in spite of a fixed arterial  $P_{CO_2}$ ,

the chemoreflex respiratory response to hypoxia was, in part, counteracted by a fall in central stimulus level, brought about by hypoxic cerebral vasodilatation. Hornbein and Roos (478) 1960, and Hornbein, Roos and Griffo (479) 1961, have studied the transient effect of sudden mild hypoxia on respiration in cats. Recent studies of carotid body chemoreceptor activity in these animals show that the activity of these organs increases greatly over a range of alveolar  $P_{O_2}$ , considerably higher than the alveolar  $P_{O_2}$  of 50–60 mm Hg which is known to produce an increase in ventilation in the steady state. In an attempt to explain this discrepancy between chemoreceptor activity and ventilation, the transient ventilatory response to two breaths of a low oxygen mixture was observed and correlated with the alveolar  $P_{O_2}$  during this brief hypoxic stimulus. A transient increase in ventilation could be detected at an alveolar  $P_{O_2}$  of 93 mm Hg, that is, considerably higher than the highest  $P_{O_2}$  known to increase ventilation during the steady state. These results were interpreted as evidence of an increased chemoreceptor drive when alveolar oxygen tension was lowered only slightly below that existing at sea level. At relatively high alveolar oxygen tensions the effect of chemoreceptor activity on ventilation is inhibited by other factors which only fully appear after several breaths.

Honda, Natsui, Hasumura and Nakamura (477) 1963, examined threshold alveolar arterial  $P_{CO_2}$  ( $PT_{CO_2}$ ) for the respiratory system in acute hypoxia in anesthetized dogs by observing phrenic nerve discharges. The authors found that the lower the  $P_{O_2}$ , the lower the  $PT_{CO_2}$ . The relationship between the  $PA_{O_2}$  and the  $PT_{CO_2}$  was curvilinear,  $PT_{CO_2}$  showing an abrupt fall in the range of  $PA_{O_2}$  of 30–60 mm Hg. The hypoxic respiratory drive was extinguished by sufficiently lowering the alveolar  $P_{CO_2}$ , showing that the respiratory drive continues to be attributable to  $P_{CO_2}$  or  $cH$  even during intense hypoxia. It was inferred that a positive interaction between  $P_{O_2}$  and  $P_{CO_2}$  or  $cH$  stimulus for ventilation exists when  $PA_{O_2}$  falls below about 70 mm Hg. Since chlorpromazine has been reported to suppress chemoreceptor activity, Schopp (488) 1958 investigated the action of chlorpromazine on the respiratory response to hypoxia. It was

assumed that one might anticipate that stimuli which act at the chemoreceptor site should be less effective after the administration of chlorpromazine. Dogs were anesthetized with chloralose (70 mg/Kg body weight). Respiratory activity was recorded by allowing the expired air to pass through a gas meter. The respiratory response to nine percent oxygen in 91 percent nitrogen was determined in 16 animals. The response to nine percent oxygen was again determined in eight animals 30 minutes after intravenous injection of chlorpromazine (5 mg/kg of body weight) and in six animals 30 minutes after a control injection of Ringer solution. After the injection of chlorpromazine, the increase in volume of expired air in response to hypoxia was about 2.5 liters greater than before injection, while after giving Ringer solution the response to hypoxia was similar to that observed before the injection. Thus a decrease in respiratory sensitivity to hypoxia which might be anticipated on the basis of the reported suppression of chemoreceptor activity after chlorpromazine, was not evident, but rather a greater respiratory response was observed.

Daly, Lambertsen and Schweitzer (471) 1953 have investigated central nervous control of bronchomotor tone in the dog. A technique of perfusing the brain through the common carotid or vertebral arteries with either blood from the left auricle or mixed venous blood from the right auricle is described. Changing the perfusion from arterial to mixed venous blood caused bronchoconstriction. This response was potentiated by eserine and abolished by atropine, and also by section of the cervical vagosympathetic nerves. As the carotid sinus regions are denervated, the responses were considered central in origin. An analysis of the bronchoconstrictor effect of mixed venous blood has been made by changing the perfusion from arterial blood to blood equilibrated with various gas mixtures in the isolated perfused lungs of a second dog. Passing either anoxic and/or hypercapnic blood through the brain causes bronchoconstriction. Hypocapnic blood causes bronchodilatation, an effect which was considered to be due to a diminution of vagus tone. It was concluded that the normal carbon dioxide tension of the blood contributes to the maintenance of vagal bronchomotor tone.



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## 8. ALIMENTARY TRACT

In general, the effects of hypoxia is to reduce the activity of the gastrointestinal tract. This applies also to conditioned salivation as shown by Malméjac and Plane (490) 1952. These authors placed dogs in an atmosphere containing 9-10 percent oxygen which resulted in a rapid diminution of conditioned salivation reflexes. Salivation was maintained if the oxygen was increased to 14 percent. In fact, at this level salivation was often augmented.

490. Malméjac, J. and P. Plane. Etude, à l'aide du réflexe conditionnel salivaire chez le chien, de dysfonctionnements nerveux supérieurs consécutifs à des agressions diverses: aspects techniques et physiologiques. *Bull. Acad. Nat. Med.*, Paris, 1952, 136: 24-28.

## 9. METABOLISM

Generally speaking, decrease of oxygen tension in the inspired air causes a decrease in oxygen consumption accompanied by a decrease in body temperature and an accumulation in the body of particles of incomplete oxidation. The literature indicates a considerable variation in the oxygen consumption rate of man and animals during hypoxia, and both increases and decreases have been found. Hypoxia also results in a mobilization of blood sugar with a drainage on glycogen stores. There may be a decrease of ketone bodies and total fats as well as lipid phosphorus. Bile secretion may be at first accelerated and then decreased; pancreatic excretion may also be decreased. In human subjects there may be a reduction in daily urinary secretion of ascorbic acid due to increased utilization. There may also be a temporary increase in the excretion of sodium, potassium and fluoride. In prolonged mild hypoxic situations increase of 17-keto steroids may be decreased. There may also be a decrease in excretion of amino nitrogen. Hypoxia

may also result in increased secretion of epinephrine.

The effects of hypoxia on brain metabolism may be serious and complicated. For a review of these effects, McFarland (510) 1952, may be consulted. This author concludes that sensory and mental impairment under experimental conditions of hypoxia may be attributed to diminished partial pressure of oxygen in the blood being delivered to nervous tissues; the changes are of cellular rather than of circulatory origin. Albaum, Noell and Chinn (491) 1953, explored changes in metabolite concentrations of various portions of the rabbit brain during progressive stages of anoxia and correlated these with electrical measurements of function. Disappearance of function and the inexcitability of all measurable elements during anoxia were associated with a moderate decrease of ATP, phosphocreatine and glycogen. Disappearance of ATP was more rapid than that of phosphocreatine. Loss of spontaneous electrical activity during early stages of anoxia occurred before significant changes in chemical constituents could be detected. Urethane controls had a higher level of ATP than the unanesthetized animals. There was a significant decrease of ATP during all stages of anoxia. Different regions of the forebrain showed no differences in ATP level nor in the depletion under anoxia. The level however was lower in the mesencephalon and the medulla and depletion occurred more slowly. In a study of metabolic processes in the brain at normal and reduced temperatures under anoxic and ischemic conditions, Thorn, Scholl, Pfeleiderer and Mueldener (519) 1958, studied rabbits under conditions of ischemia and anoxia. Experiments were performed at normal and at lowered body temperatures (26°C.). Ischemia was induced by means of a cuff around the animal's neck and anoxia was obtained by ventilation with a mixture of nitrogen and carbon dioxide. The brains were removed with a cooled spoon and frozen in liquid air. Deproteinized extracts served for the determination of ATP, ADP, fructosediphosphate (FDP), dihydroxyacetone phosphate (DAP), pyruvic acid (BTS), lactic acid (MS), inorganic phosphate, alanine, glutamic acid and aspartic acid, which were partly estimated by optical enzymic methods. The shock of decere-

bration momentarily affected the concentrations of inorganic phosphate, creatine phosphate (PKr), FDP, ATP and ADP. The concentration of inorganic phosphate was raised, and PKr and ATP lowered. The extent of this immediate change could be measured by comparison with the value obtained after freezing the whole head with the brain *in situ*. Similar changes were obtained under anoxic and ischemic conditions. The inorganic phosphate increased in ischemia and in anoxia. In anoxia and in ischemia the ADP concentration initially increased and decreased later. Thorn and Heimann (518) 1958 found that during anoxia ammonia concentration in the brain increased. In a study of the tolerance to anoxia and development of cerebral succinic dehydrogenase and cytochrome oxidase activities in the rabbit, Cassin and Herron (498) 1961, have reported that newborn rabbits tolerate 30–35 minutes of anoxia, while adult rabbits withstand anoxia for only three to five minutes. In order to secure further information as to the mechanisms of resistance of the newborn animal to anoxia as compared with the adult, the authors studied changes in the cerebral succinic dehydrogenase and cytochrome oxidase activities in rabbits varying in age from less than 24 hours to adulthood. It was found that succinic dehydrogenase and cytochrome oxidase activities were very low at birth, but gradually increased until the 15–18th post-natal day. It was found that between the age of 15 and 18 days there was a critical period in the development of these enzymes, and at this period adult levels of activity were reached. It was found that at this critical period in age the tolerance of the developing rabbit to anoxia reached the adult level. This increase in oxidative enzyme activity is in agreement with the hypothesis that the metabolism of the mammal is transformed from a predominantly anaerobic condition at birth to an aerobic condition with maturation.

The effects of hypoxia on the myocardial metabolism of intact dogs have been reported by Hackel, Goodale and Kleinerman (505) 1954. In these studies the dogs were subjected to air mixtures containing ten percent, five percent and zero percent oxygen. It was found that coronary flow and myocardial oxygen extraction was significantly increased during oxygen lack. The



result of this was that the total left ventricular oxygen consumption was maintained during the administration of 10% oxygen as well as 5% oxygen. With 10% oxygen there was little change in carbohydrate uptake by the myocardium. Administration of 5% oxygen resulted in increased arterial levels of lactate and pyruvate and significant decreases in arterial venous differences and coefficients of extraction of pyruvate, lactate and glucose. At the same time the total utilization of these substances was maintained. Complete oxygen deprivation resulted in negative arterial venous or arteriovenous differences for lactate, and greatly decreased values for pyruvate. Doring, Kammermeier and Byon (499) 1962, found that acute asphyxia resulted in a rapid dilation of the guinea pig's heart *in situ*. A maximal cardiac dilatation was usually reached within one minute of asphyxia whereas cardiac arrest occurred after six to seven minutes. If normal respiration was then resumed, tone and contractility recovered completely within one minute, provided that the previous asphyxia had not endured longer than four minutes. Cardiac dilatation was accompanied by a corresponding breakdown of phosphocreatinine ( $1 \mu\text{M}$  CP/gm in dilated hearts as contrasted with eight or nine  $\mu\text{M/g}$  in the controls). During recovery phosphocreatinine concentration was restored to normal. A similar correlation between dilatation and phosphocreatinine breakdown was found after nitrogen or carbon monoxide respiration, and in hearts poisoned with cyanide and other substances such as 2, 4-dinitrophenol. There were relatively small changes in ATP during the initial phase of dilatation. Merrick and Ellis (512) 1952, and Merrick (511) 1954, have studied changes in cardiac glycogen in normal goldfish subjected to acute anoxia induced by bubbling pure nitrogen gas through the water in which the fish were swimming and maintaining the dissolved oxygen in the water at 0.58 ppm by keeping the water under nitrogen. It was found that displacement of dissolved oxygen by nitrogen caused no significant change in pH or salt balance in the well buffered tap water that was used. All of the control and revived fishes were carried in water of 7.4 ppm oxygen. It was found that the cardiac glycogen of the controls was 23.6 mg/gm. of cardiac tissue. This is the highest

normal value yet reported for any vertebrate. Acute distress developed in these fishes abruptly transferred to the low oxygen water in approximately five hours. The end point for acute anoxia was set at 15 minutes after opercular movements ceased. It was found that in the anoxic series little or no change in cardiac glycogen occurred before the symptoms of acute anoxia appeared. However, with the onset of incoordination and irregular opercular movements, cardiac glycogen fell rapidly to an average of 2.6 mg./gm. Cardiac glycogen did not return to normal in less than three hours or more in anoxic fishes revived in fresh water, although after six hours cardiac glycogen again approached the values for the controls. These anoxic and recovery experiments suggest that the high resistance of the goldfish to anoxia may be associated with a high glycogen content of the heart. It was concluded that complete removal of cardiac glycogen is not a prerequisite to the failure of the respiratory and cardiovascular mechanisms during fulminating anoxia. These experiments considered collectively support the view that cardiac glycogen is an emergency standby utilized by the heart during periods of anoxic stress. With regard to fatty acid metabolism in the heart subjected to hypoxia, Evans and Jacobs (500) 1964, using the isolated rat heart, concluded that mild hypoxia impairs oxidations of fatty acid and increases formation of triglyceride and phospholipid. Severe hypoxia inhibits oxidation and triglyceride formation and favors accumulation of phospholipid and non-esterified fatty acid in heart muscle.

Bassi and Bernelli-Zazzera (494) 1955, have studied the metabolism of vacuolated cells following hypoxia in adult albino rats. In these studies appreciable vacuolation of cells after hypoxia was present only in the liver. It appeared that the respiratory quotient significantly lowered in the vacuolated cells as compared with the controls. Oxygen uptake of octanoic-oxidase and succinic-oxidase activities remained unchanged.

Since the autonomic nervous system and the adrenal glands participate in physiological adjustments to many situations which disturb homeostasis, McElroy and Spitzer (509) 1961, performed studies to determine the response of plasma free fatty acid during hypoxia, a stress

which stimulates the sympatho-adrenal axis. These studies were carried out in fasting adult mongrel dogs of both sexes. Hypoxia resulted in an increase in blood sugar, the mean blood pressure, heart rate, femoral venous-arterial free fatty acid concentrations, respiratory minute volume, and tidal volumes. The hypoxia was produced by breathing eight percent oxygen in nitrogen for 15 minutes. The respiratory rate and minute volumes doubled over control levels although the tidal volume increased very little. The authors pointed out that recorded changes in these animals resemble qualitatively those observed after injection of epinephrine or during emergency response to stress. The changes were reproducible when the animals were rendered hypoxic a second time. Rises in free fatty acid and glucose levels closely follow circulatory compensatory responses. To determine the mechanism responsible for these results, similar experiments were performed on dogs with both adrenal glands occluded from the circulation. In these latter studies the blood sugar did not rise and the free fatty acid elevations were very slight. To differentiate changes in free fatty acid as being mediated through hormones secreted by the adrenal medulla or adrenal cortex, a group of dogs were tested for hypoxic responses before and after bilateral sectioning of splenic nerves. The changes observed in the intact animals were greatly reduced after splenic sectioning.

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## 10. ENDOCRINES

It has been long known that hypoxia may elicit sympatho-adrenal responses. Gerst, Naaman, Rodil, Wolf and Root (523) 1961, have attempted to establish an arterial blood oxygen tension threshold at which a significant sympatho-adrenal response is initiated. In these studies anesthetized dogs with chronically denervated hearts, after a control period, were given gas mixtures containing low oxygen to breathe. Respiratory pattern, arterial blood pressure, electrocardiogram and esophageal temperature were recorded continuously. Arterial blood samples were analyzed for carbon dioxide and oxygen content, oxygen capacity, hemoglobin concentration and pH. Arterial blood  $P_{O_2}$  was determined by reference to an oxyhemoglobin dissociation curve for dog blood. There was no significant increase in the rate of the denervated heart of the spontaneously breathing dog until the  $P_{O_2}$  fell to approximately 55 mm Hg. Below this level there was a relatively sharp increase in heart rate over the control level: 11% at a  $Pa_{O_2}$  of 40 mm Hg, 35% at a  $Pa_{O_2}$  of 28 mm Hg. The acceleration was ascribed by the authors to release of catecholamines, although this was considered to require confirmation. Since the  $Pa_{O_2}$  at which an increase in heart rate occurs is within the physiological range, it was concluded that the

sympatho-adrenal response probably serves as a compensatory mechanism in a stressing situation. The stressful effects of oxygen deficiency upon adrenal cortical functions have been pointed up by Aschan (521) 1953, in a study on white rats exposed to oxygen deficiency for two hours, resulting in a significant reduction of ascorbic acid contents of the adrenal glands.

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## 11. TEMPERATURE

Hypoxia acutely depresses the metabolic response to cold in newborn rabbits as reported by Blatteis (530) 1963. Experiments conducted to elucidate this mechanism revealed that the increased rate of oxygen consumption at 25° C. was initially depressed by 10 percent oxygen but reverted towards pre-hypoxic levels during the next four hours, usually with vigorous shivering. Previous exposure to hypoxia alone did not obviate the acute hypoxic depression of the metabolic response to cold. Neither did pre-exposure to cold alone unless shivering was already present. Bilateral section of the carotid sinus and/or vagus nerves had no effect on the thermogenic response to cold or its depression by hypoxia, but catecholamines caused some increase during cold and

hypoxia. These results suggest that the acute depressive reaction of hypoxia on the metabolic response to cold may be due to interference with some rate-limiting physiological process rather than a specific effect of hypoxia, as for instance, on the chemoreceptors. Bullard and Kollias (532) 1962, have studied the primary effects of hypoxia on the thermal regulatory mechanisms and the relation of hypoxic alteration of body temperature and hypoxic tolerance. They have also compared hypoxic and thermal responses in different mammalian species. The white rat at 23° C. had the same depression of oxygen consumption with both hypoxia ( $P_{O_2} = 75$  mm. Hg) and chlorpromazine treatment (25 mg./Kg body weight), while the cooling rate with chlorpromazine treatment was three times greater than that with hypoxia. When white rats and ground squirrels (*Citellus tridecemlineatus*) were exposed to cold (10° C.) and hypoxia ( $P_{O_2} = 75$  mm. Hg) the ground squirrel showed less metabolic depression but greater body cooling. The ground squirrel had greater hypoxic tolerance even at higher temperatures, so this was not due to greater body cooling. Similar studies were done at White Mountains, California, at an altitude of 12,250 feet, with altitude adapted rats and native ground squirrels (*Citellus lateralis*). The hypoxia of *C. lateralis* was much greater than that of the altitude adapted rats and sea level rats and ground squirrels. The *C. lateralis* in hypoxia was able to maintain a higher body temperature, higher oxygen consumption, and a higher heart rate than the other species. The authors concluded that the high tolerance of the altitude squirrel is related to a greater capability for compensatory activity in hypoxia rather than greater tolerance to functional and thermal depression.

In a study of approximately 20 cats, anesthetized with pentobarbital sodium adjusted so that shivering was absent or vigorous Hemingway and Birzis (353) 1955-56, subjected the cats to hypoxia by progressively decreasing the percentage of oxygen in an inhaled nitrogen-oxygen mixture. It was found that decreasing the oxygen percentage between 21 and 13 percent had no effect on shivering. Between 13 and 8 percent shivering decreased until it was abolished and oxygen consumption rate decreased to the non-

shivering value. With non-shivering decerebrate cats, as the inhaled oxygen was progressively decreased, oxygen consumption rate did not change until the range of 6-3 percent oxygen was reached, after which gasping respiration and apnea supervened.

Observations on small animals, such as rats, guinea pigs, as well as in man, indicate that mild degrees of hypoxia lower the physiological resistance to cold. This seems to be a characteristic of homothermic organisms and has been confirmed in the dog by Hemingway and Nahas (534) 1952. These investigators measured oxygen consumption rate, respiratory quotient, ventilation rate and rectal temperature in selected, trained dogs subjected to air, oxygen-nitrogen mixtures of 6-16 percent oxygen for one hour, and finally air. During the early part of the hypoxia interval there was a sharp rise in minute volume of respiration and respiratory quotient. Oxygen consumption rate at first fell to sub-normal values and then slowly rose to approach normal basal values. In the third period, that is to say the post-hypoxic period, oxygen consumption rate was above normal. The rectal temperature fell during the hypoxic period but rose rapidly after air breathing was resumed.

Lim and Luft (536) 1960, have investigated the effect of moderate hypoxia (tracheal  $P_{O_2} = 65$  mm. Hg) on thermoregulation under neutral (27.5° C. relative humidity of 30 percent) and hot (40.5° C. relative humidity 80 percent) conditions over a period of two hours in healthy male subjects on different days with similar control periods of breathing air. It was found that neither the course of rectal and mean skin temperatures was significantly affected nor was the metabolic rate altered by the hypoxia imposed. The intensity of shivering estimated from oxygen consumption was the same (2.5 times control level) in the cold with or without hypoxia. Weight loss due to perspiration was essentially equal whether breathing air or the hypoxic gas. Notable differences were observed in cardiorespiratory response to heat and cold during hypoxia. In the heart with hypoxia the heart rate increased in a synergistic rather than an additive fashion, and the diastolic pressure was much lower. In similar experiments, Bullard (531) 1961, found with human subjects



an increase in shivering activity and oxygen consumption 30 minutes after exposure to 5° C. during breathing of 10 percent oxygen. This increase in shivering and oxygen consumption usually subsided after 15 minutes. The recovery periods after hypoxia breathing were often characterized by greatly decreased shivering activity. The author found that both heart rate and pulmonary ventilation rates were higher in hypoxic cold exposed subjects than in hypoxic subjects in a room at 30° C. It was hypothesized that the shivering increase is a release phenomenon.

The work of Miller, Miller and Farrar (537) 1954 in guinea pigs subjected to asphyxia indicates that environmental cooling increases the tolerance of the animal to the asphyxial conditions.

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## 12. KIDNEY

The postnatal development of diuresis in response to hypoxia has been studied by Adolph and Hoy (540) 1955. Exposure to low oxygen mixtures in infant rats ( $P_{O_2} = 42-46$  mm. Hg)

induced within two minutes an anuria or marked oliguria, followed after 15-30 minutes by diuresis. The diuresis often persisted for 30-60 minutes after room air again surrounded the animals. At two days of age the diuresis was less pronounced than at five days of age, and the urinary chloride dilution was less. Hence this response, like some other urinary diuresis and clearances, developed postnatally. In adult animals an injection of epinephrine sometimes induced a diuresis similar to the diuresis of hypoxia, but no diuresis was found in infant rats of 2-9 days of age given epinephrine subcutaneously unless water was also administered. The postnatal development of hypoxic diuresis appeared to parallel that previously found for the water diuresis and the authors concluded that these two may share common factors. The interrelationships of renal blood flow and blood oxygen saturation during 8-11 percent oxygen breathing were investigated by Balint, Fekete, Gomori and Nagy (541) 1960. These studies were carried out in chloralosed dogs. Renal blood flow measured directly by PAH clearance technique was seen to decrease during hypoxia at blood saturation levels below 50 percent. Blood oxygen saturation showed an inverse linear relation with renal resistance and a direct linear relationship with the renal fraction of total blood volume. A significant increase in minute volume was observed only when blood oxygen saturation fell below 50 percent. The response of the kidney to hypoxia created by a perfusion with venous blood obtained from the right ventricle was studied by Selkurt (546) 1953 in anesthetized dogs. A pump aided in supplying the blood with an adequate head of pressure. The advantage of the method was that it permitted a specific hypoxia to be imposed upon the kidney with minimal disturbance to the organism as a whole. Blood oxygen content in different experiments varied from 6.7-15.9 volumes percent during venous perfusion (average 10.7). The most consistent response was an increase in PAH clearance, in one instance as great as 92 percent, but averaging 22 percent. Renal vascular resistance showed a typical reduction during hypoxia. The nature of this hyperemia has not been clarified. Creatinine clearance characteristically decreased by an average of 10 percent. The net

effect therefore was a reduction in the filtration fraction. The usual response in the excretion of sodium, potassium and water, was an increase. Because excretion increased while filtration rate declined in several experiments, the conclusion was drawn that hypoxia had slightly impaired the tubular reabsorptive processes of these substances.

Lowrance, Nickel, Smythe and Bradley (543) 1956 have studied renal function in the harbor seal during the asphyxia of anoxia and during anoxic anoxia produced by inhalation of 10 percent oxygen in nitrogen. Both apnea and anoxia resulted in a diminution of glomerular filtration rate and renal plasma flow. Urine volume decreased in these experiments and the total output of sodium and potassium was diminished. Urinary concentration of sodium tended to fall, whereas the urinary concentration of potassium usually remained unchanged. Tubular reabsorption of water decreased relative to filtration. The influence of vagal activity, respiratory movements and cardiac rate and rhythm on renal function could be excluded. The authors came to the conclusion from these experiments that apnea and anoxia have comparable effects on renal function in the seal. Selkurt (545) 1952 found that the creatinine/inulin clearance ratio remains close to one during hypoxia in anesthetized dogs with blood oxygen content as low as 5.5 volumes percent resulting from inhalation of an 8 percent oxygen mixture. Since the absolute clearance value did not increase it was concluded that the creatinine clearance remains an adequate measure of glomerular filtration rate under these conditions.

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### 13. EFFECTS OF CARBON DIOXIDE ON HYPOXIA

The interaction of hypoxia and hypercapnia at the carotid bodies in chemoreflex stimulation of breathing has been studied by Otey and Bernthal (550) 1960. In this investigation arterial blood from one anesthetized dog (donor) was continuously circulated through the vascularly isolated carotid region of another dog (recipient). It was then returned to a vein of the donor. Breathing was continuously recorded by spirometer and end-tidal  $P_{\text{CO}_2}$  and  $P_{\text{O}_2}$  were under control while being monitored by infra-red and paramagnetic analyzers respectively. Hypercapnia in combination with normal end-tidal  $P_{\text{O}_2}$  in the donor evinced only slight increase in breathing by the recipient. When however hypercapnia of identical degree was superimposed upon a pre-existing hypoxia of the donor, there occurred a significant increment in the hyperpnea of the recipient beyond that due to the carotid body hypoxemia alone. Thus combined, hypercapnia and hypoxia at the carotid bodies of the recipient produced a substantially greater increase in breathing, about 100 percent on the average, but sometimes as much as 350 percent. This was more than would be predicted by merely adding the increase due to separately imposed hypoxia to the increase due to separately imposed hypercapnia. The authors concluded that the carotid chemoreceptors are the site of a positive interaction between these two agents, such that the stimulating action of one is enhanced by the coexistence of the other.

Cormack, Cunningham and Gee (547) 1957, have shown in human subjects that with higher levels of  $P_{\text{CO}_2}$  anoxia causes significantly greater responses in respiration, frequency, ventilation, etc. These authors' results contradict the hypothesis that respiratory stimuli do not interact.

Considerations of the effects of carbon dioxide upon hypoxic reactions raises the important



question of the value of the administration of carbon dioxide under conditions in which artificial respiration is indicated. If carbon dioxide is administered during artificial respiration, the  $P_{CO_2}$  in the lungs and well-circulated organs may be raised to highly abnormal levels unless a considerable further increase of ventilation can be induced. Under first aid conditions the rescue worker never knows the initial levels of carbon dioxide in the body of the subject, nor the ventilatory volumes he is producing. The administration of carbon dioxide under these conditions is therefore uncontrolled and uncontrollable, and in many cases is apt to cause a dangerous intensification of carbon dioxide accumulation and intoxication. These points have been made by Donald and Paton (548) 1955. These authors emphasize the dangers of high concentrations of carbon dioxide in the body. These dangers include depression of the central nervous system, especially the respiratory areas, vasomotor depression with peripheral vasodilatation, hazardous cardiac arrhythmias, and fall in body temperature. For these reasons the authors recommend that in first aid practice carbon dioxide should not be administered with oxygen in the resuscitation of subjects requiring and receiving artificial respiration.

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#### 14. ACCLIMATIZATION

The mechanisms of acclimatization to hypoxia are not yet fully understood. Reference may be made to a review of the subject by Stickney and Van Liere (554) 1953. These authors have discussed an integrated series of adaptation which

characterized acclimatization to chronic exposure to low oxygen tension in the inspired air. These adaptations involve various organ systems and tissues of the body. Increased ventilation of the lungs elevates appreciably the oxygen tension in the alveoli while simultaneously reducing the carbon dioxide tension. The adaptation is complete when alkaline reserve has been reduced so that blood pH is brought within the normal range. At this point respiratory control is more or less completely based in the central nervous system respiratory areas and the chemoreceptors have little if any part in the picture. According to the authors the adrenal cortex may have a heightened activity in this state of acclimatization, but it is not apparent. Its chief role presumably has been discharged in the early adaptation of the acute phase of exposure while acid-base balance was being adjusted and while increased demands were being made on carbohydrate metabolism. While cardiac output may have been increased during the early adaptive phase, in the completely adjusted organism the output is not increased over the pre-exposure value, either at rest or in exercise. There may be a minimal amount of cardiac hypertrophy involving mainly the right heart. The cause for this is not apparent. There is greatly increased vascularization of many tissues resulting in improved diffusion of oxygen nutrients and metabolites. The oxygen carrying capacity of the blood is greatly increased. There is no evidence that the resting metabolic rate is changed and growth and body weight remain normal. The question of increased muscle myoglobin content in the acclimatized state remains in doubt. Capacity for work in the acclimatized subject has been reported to be equal to that of the comparable sea level resident. Renal and gastrointestinal physiology remain normal. The authors also state that the finding of reduced scores in reaction time tests remains unchallenged. In an acclimatized person fertility and reproductive powers remain normal.

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## 15. PATHOLOGY

Meyer (569) 1956, has reviewed neuropathological findings in the cases of six human beings who died from anesthesia. On histological examination severe lesions were found in all cases in the cerebral cortex, Ammon's horn and cerebellar cortex. The white matter was affected in one case. The basal ganglia were damaged in most cases while the thalamus, reticular zone of the substantia nigra, the corpus Luysii and dentate nuclei involved in some cases. There were no definite changes seen in the hypothalamus, red nucleus and the compact zone of the substantia nigra or the geniculate bodies and inferior olives.

Comparing human cases with experimental data on cats, lesions the same as in human beings were found in these animals.

Edstrom and Essex (563) 1956, in a study of dogs subjected to respiratory hypoxia found no noticeable swelling of the brain or increased intracranial pressure clearly attributable to cerebral edema within several hours after the hypoxic period.

Local anoxia of brain tissue induced by oil or starch emboli consistently caused very rapid swelling of the brain and increase in intracranial pressure in the absence of any obvious systemic hemodynamic change.

In order to study the changes of nerve cells in the cerebral cortex following acute anoxia, Hager, Hirschberger and Scholz (564) 1960, exposed Syrian hamsters repeatedly to pure nitrogen atmospheres and low atmospheric pressure. Another group of animals was treated with potassium cyanide. A special method of osmic acid fixation by perfusion was developed to avoid a postmortem autolytic breakdown of the ultrastructures. The changes in the submicroscopic structures regularly involved the cell body. The nucleus was generally better preserved. The mitochondria were swollen and the mitochondrial

cristae appeared broken and in some of the swollen mitochondria they had more or less disappeared. In the outer zone of the perikaryon, the granular and lamellar components of the endoplasmic reticulum were also disintegrated. These ultramicroscopic findings suggest the interpretation that severe acute hypoxia causes a rise of intracellular osmotic pressure due to an increasing concentration of osmotically active components.

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## B. LOW OXYGEN TENSIONS DUE TO DECOMPRESSION

### 1. NERVOUS SYSTEM

General effects of decompression upon the nervous system have been summarized by Luft and Noell (586) 1955-56, and Grandjean (582) 1954, and Donaldson, Carter, Billings and Hitchcock (578) 1960. Luft and Noell examined cerebral manifestations of hypoxia during and after exposure to a barometric pressure of 68-70 mm. Hg by rapid decompression while breathing oxygen in two human subjects in a series of tests ranging from 6-18 seconds duration. The following rapid sequence of neurological events was observed: 1) a state of automatism which ensued 13-15 seconds after decompression and exposure of more than 16 seconds duration. The subjects behaved as if confused and incapable of proper interpretation of judgment. There was amnesia during this phase. The EEG changes during this time were slight and consisted mainly in the activation of normal rhythms. 2) There was then a phase of 'arrest' initiated by sudden loss of consciousness at about 17-19 seconds. Almost all spontaneous movement ceased, the eyes became fixed and glaring,

and this was followed shortly by conjugated upward rolling of the eyeballs. Posture was maintained but respiration was arrested. The duration of this phase did not exceed three seconds. The EEG lacked specific changes, but there was a continuous increase in slow wave activity. 3) There was then a phase of failing posture, beginning with a slow drooping of the head of the sitting subject seen 19-20 seconds after exposure for at least 12 seconds. The generalized weakness was intermittent and was interrupted by brisk, rhythmic muscular movements which temporarily counteracted falling. The EEG deteriorated progressively, as evidenced by dominance of abnormally slow frequencies and temporary absence of brain activity. The authors established certain analogies between the observed phenomena and changes in consciousness during epileptic seizures. They considered that the pattern of anoxic failure depends upon the loss of normal function in major integrating systems of cerebral activities. The net anoxic survival time of the most sensitive of these systems appears to be 4-5 seconds, and of that which determines loss of comprehension (unconsciousness) 7-8 seconds. These figures were compared with those obtained in other circumstances leading to sudden impairment of brain oxygenation.

Grandjean concluded that the central nervous system is stimulated by altitudes up to 3500 meters and is then depressed at higher regions. This stimulation of nervous function may be the result of general emergency reactions of the autonomic nervous system which regulates adaptation of the body to first degrees of oxygen lack. In Grandjean's studies healthy human subjects were studied at low altitudes of 560 or 800 meters and then taken to an altitude of 3450 meters on the Jungfrauoch. They remained at altitude for two to three weeks. Thresholds of cutaneous sensitivity were lowered at altitude in most of the subjects. Thresholds of gustatory sensitivity to glucose, NaCl, tartaric acid, quinine, were lowered in all subjects examined at altitude. There was also increased visual sensitivity and lowering of the thresholds for the knee-jerk reflex. Administration of pure oxygen rapidly raised the thresholds at altitude for cutaneous sensitivity and knee-jerk reflex. Carbon dioxide inhalation had no effect. At altitude there was

a decrease in the amplitude of equilibratory movements. The consensual light reflex of the pupil was shortened at altitude, as were reaction times to optic stimulation.

The effect of altitude and oxygen upon primary taste perception has been examined by Finkelstein and Pippitt (580) 1958. These authors studied the effects of breathing 100 percent oxygen at a simulated altitude of 25,000 feet upon the taste sensitivity of young male adults. The study was performed to determine whether taste perception levels, taste identification levels, or ability to identify tastes, are effected by altitude, or by breathing pure oxygen. Motivation for this study was derived from differences noted in food acceptability on the ground and on high altitude flight situations. No effects of altitude or breathing pure oxygen on primary taste sensations were found which could account for these differences. An inability to identify taste, both on the ground and at altitude, was observed. From the results of this study the authors conclude that taste test procedures should not include questions that assume a subject's ability to identify the primary tastes, particularly of sour and bitter.

In 1953 Tonndorf (588) carried out laboratory experiments on human subjects to determine the combined effect of noise and hypoxia upon auditory threshold. Hypoxia was found to enhance the effect of noise.

Ernsting, Gedye and McHardy (579) 1961 have observed EEG changes produced by brief periods of decompression at levels from 560–155 mm. absolute pressure. Reference may also be made to a paper by Woolley (590) 1964 in which a report was given of rats chronically implanted with bipolar electrodes in the lateral olfactory tract for stimulation and in the prepyriform cortex for recording. Prepyriform (PPC) responses were evoked by single shock (4/sec.) stimulation of the lateral olfactory tract (LOT) and were averaged with a Mnemotron C.A.T. before, during and after two hours of exposure to simulated high altitudes. Averages of 150 responses were subject to spectral (amplitude vs. frequency) analysis with the aid of computers. In each of five rats control spectra were characterized by a dominant component with a peak amplitude between 44 and 53 cycles per second. Other peaks

were found at 1, 11, 19–25 and 65–100 cps. They usually had amplitudes less than half that of the dominant frequency. Exposure to 18,000 feet altitude resulted in prompt decreases in the frequency and amplitude of the principal components of approximately 12 and 40 percent respectively. Similar changes were observed during exposure to 12,500 feet simulated altitude. Additional studies showed that the latency between stimulus and the beginning of the evoked response was significantly prolonged at altitude. The data suggested that conduction rate may be decreased or synaptic transmission delayed during altitude exposure.

Heim and Timiras (584) 1964 produced spinal cord convulsions in rats at sea level and in rats of the first generation ( $F_1$ ) born at 12,470 feet. At 11 and 28 days of age rats of both groups were decapitated at the cervical region. The spinal cord was stimulated by a needle electrode inserted into the cervical cord and the anode was attached to exposed tissue of the neck. Square-wave stimuli, supramaximal with respect to voltage and duration, were obtained from a Grass stimulator at 100 pulses per second. Ten seconds after decapitation the cord was stimulated and the durations of hindlimb flexion and extension were recorded in both groups of rats. Mean values  $\pm$  S.E. for the duration (seconds) of the tonic phases of convulsion in 11 day old controls and  $F_1$  rats were respectively: flexion  $\pm$  0.10 and  $1.30 \pm 0.07$ , and extension  $8.85 \pm 0.30$  and  $11.15 \pm 0.12$ ; in 28 day old controls and  $F_1$  rats: flexion  $2.15 \pm 0.15$  and  $1.48 \pm 0.1$  and extension  $4.07 \pm 0.5$  and  $6.60 \pm 0.38$ . The shorter flexion and longer extension in both age groups of rats born at high altitudes indicated to the authors an increased activity of the spinal cord. It was suggested that hypoxia and/or hypercapnia occurring at high altitude affects spinal reflex activity and thereby influences the functional development of the central nervous system. In 1963 Heim and Timiras (583) had carried out experiments on rats indicating that although brain maturation is delayed at altitude, greater convulsability is exhibited by rats developing at altitude than at sea level.

That performance of human subjects at 20,000 feet is inferior to performance at ground level was indicated by experiments of Lansberg (585)



1959. This investigator administered stereophonic discrimination tests to six experienced pilots under the following experimental conditions: 1) at ground level, 2) at 20,000 feet without oxygen, 3) at 20,000 feet with oxygen, and 4) again at ground level. Signal tones of 750 c.p.s. and 2,500 c.p.s. were presented over a set of headphones at a sound pressure level of 70 decibels during one second, followed by a four second pause. A time delay line, which could be operated in 25 microsecond steps, dispatched a signal the right or left ear, or to both simultaneously, and the subjects were asked to indicate on paper whether there was an impression of lateralization to the right side, to the left side, or no lateralization. The tabulated results showed considerable divergence between the individuals and indicated, as has been said, that the performance at 20,000 feet was inferior to that at ground level. The author stated that further exploration of the effect of the time interval between tests at 20,000 feet and further evaluations of individual susceptibility were warranted.

Malmejac and Plane (587) 1952 have studied the influence of oxygen want on functional cortical fitness by analysis of salivary conditioned reflexes in dogs. For the details of this study the original paper should be consulted.

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## 2. MUSCLE

The effects of 20,000 feet simulated altitude on myoglobin content of animals with and without exercise has been studied by Clark, Criscuolo and Coulson (591) 1952. In one group of experiments heart, gastrocnemius and diaphragm muscles of hamsters were analyzed for myoglobin content after a continuous acclimatization period of six weeks without exercise to a simulated altitude of 20,000 feet. Myoglobin values in terms of mg./gm. of wet tissue were measured. In a second group the gastrocnemius was removed from one leg before acclimatization and from the other leg at the end of the exposure period. In another series rats were exposed to a simulated altitude of 20,000 feet for six weeks and exercised for 30 minutes each day on a treadmill. Control groups were kept at ground level and exercised on a treadmill for a similar period. The results showed approximately a 200 percent increase of myoglobin in heart muscle for animals exercised during acclimatization at 20,000 feet simulated altitude as contrasted with those exercised at ground level. There was a 50 percent increase of diaphragmatic and gastrocnemius muscle myoglobin in the exercised animals at altitude as contrasted with those at ground level. Vaughan and Pace (592) 1956 have also reported an increase of myoglobin in rats taken from sea level to high altitudes (12,500 feet).

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### 3. HEART AND CIRCULATION

Under progressive hypoxia there tends to be an acceleration of the heart with alteration in systolic blood pressure, the pressure being maintained, then rising, and then gradually falling. The pulse pressure tends to remain unchanged or increases. Astrand and Astrand (599) 1958 recorded heart rate on four subjects performing muscular work: at sea level, during a three week sojourn at 14,250 feet altitude, during reacclimatization to sea level conditions, and during acute exposure in an altitude chamber. It was observed that an increase in oxygen supply during heavy work in these subjects promptly increased the heart rate well above the ceiling which had been established. This response was observed only in acclimatized subjects. After reacclimatization to sea level, when acute hypoxia in the altitude chamber was removed by switching to oxygen during work, the heart rate invariably decreased. The effect of hypoxic hypoxia and low barometric pressure on the human electrocardiogram (vector analysis) has been studied by Alifanov (593) 1961. These studies were carried out on healthy human subjects to simulated altitudes of 5000 meters while breathing either air or at an equivalent altitude of 10,000 meters while breathing oxygen. In subjects who did not tolerate hypoxia well there was an indication of increased load on the right heart. When no adverse effects resulted, the shift of the cardiac vectors to the left was accompanied by signs of increased left ventricular activity. With deterioration of the subjects' condition there was also an indication of increased load on the right heart, therefore an EKG indicating such an increased right heart load constitutes also an objective sign of deterioration of the physical condition.

Several aspects of pulmonary circulation have been studied by Rotta, Cánepa, Hurtado, Velásquez and Chávez (616) 1956 in healthy adult males living at sea level and in temporary and permanent residents at altitudes of 4,540 meters (14,900 feet). A moderate, but significant degree of pulmonary hypertension has been found in men living at high altitudes. This condition be-

ing accentuated in the permanent resident and most striking in the cases of chronic mountain sickness. The probable pathogenesis of this condition is discussed in the original paper. Peñaloza, Sime, Banchero, Gamboa, Cruz and Marticorena (614) 1963, have also studied pulmonary hypertension in healthy men born at high altitudes and living in such localities. Mild hypertension and a moderate increase of pulmonary vascular resistance and high ventricular work were found in men living permanently at high altitude. Pulmonary wedge pressure, cardiac output and heart rate did not show significant differences from similar data obtained at sea level. Changes occurring in pulmonary circulation in men at high altitudes were not quite comparable to changes described in temporary residents at high altitudes, nor with those experimentally obtained by acute hypoxia. Therefore, the effects of hypoxia upon the pulmonary circulation are related not only to the degree of hypoxia, but also seem to be related to the time of exposure to it. The augmented pulmonary vascular resistance in the high altitude dweller is related to the anatomic changes in the small pulmonary arteries and arterioles which have been described by other investigators. Functional factors such as vasoconstriction, hypervolemia and polycythemia, do not play an important role in the mechanism of pulmonary hypertension at high altitudes. The role of pulmonary hypertension in the complex mechanism of acclimatization to life at high altitude is not well understood. Apparently pulmonary hypertension would not accomplish a useful part in this mechanism. It is possible, however, that pulmonary hypertension in association with other factors, such as hyperventilation and an extensive capillary bed of the lungs, does play a part in improving the arterial oxygenation in men living permanently at high altitudes. Further studies on pulmonary circulation and pulmonary hypertension have been reported by Banchero, Sime, Peñaloza, Cruz and Gamboa (602) 1963, and Sime, Banchero, Peñaloza, Gamboa, Cruz and Marticorena (619) 1963.

Associated with pulmonary hypertension, it has also been shown by electrocardiographic and vectorcardiographic observations that dwellers at high altitudes show moderate degrees of right



ventricular hypertrophy (Peñaloza, Gamboa, Dyer, Echevarría and Marticorena (612) 1960, Peñaloza, Gamboa, Marticorena, Echevarría, Dyer and Gutierrez (613), 1961). Right ventricular hypertrophy was demonstrated, for example, by Rotta and López (617) 1959, in adult natives or long-term residents of Morococha, Peru (14,900 feet above sea level). The EKG confirms the anatomic and radiographic findings, previously obtained in normal individuals at high altitudes. The authors believe that the right ventricular hypertrophy was related to the pulmonary hypertension usually found in men at high altitudes. Studies of heart rates, at simulated altitude and at altitude, by Valdivia, Rudzik and Richardson (622) 1963, demonstrated in guinea pigs the presence of right ventricular hypertrophy in animals submitted to experimental and natural altitudes above 12,000 feet. It was also demonstrated in six animal species (guinea pigs, rabbits, dogs, lambs, pigs and steers) by Hultgren, Marticorena and Miller (610) 1963. The study of formalin-fixed heart rates demonstrated a moderate hypertrophy of the right ventricle in animals living continuously at altitudes of 10,000 to 15,000 feet altitude. These authors related the hypertrophy to pulmonary hypertension.

With regard to peripheral circulation and the effect of simulated altitude upon it, Sunahara and Girling (620) 1958, exposed normal human subjects to 225 mm. Hg absolute pressure (30,000 feet simulated altitude). Forearm blood flow was not affected by the exposure whereas hand blood flow was reduced significantly in all subjects. There was no change in heart rate. Since arterial blood pressure did not change there must have been constriction in the hand vessels. The effect appeared to be immediate and to be independent of the time spent at the reduced barometric pressure. There was considerable variation in hand blood flow response to the post exposure period. In many subjects the hand blood flow remained reduced for a considerable period, while in others it returned immediately to control values. These studies indicate to the authors that reduced barometric pressure increases sympathetic activity of the skin and blood vessels in man. On the other hand, Turner, Lambertsen, Owen, Wendel and

Chiodi (621) 1957, found in human subjects that inhalation of 8, 21 and 80 percent oxygen produced with 80 percent oxygen no change in brain circulation or cerebral vascular resistance from control levels obtained during 21 percent oxygen breathing. Inhalation of 8 percent oxygen decreased cerebral vascular resistance 29 percent and increased brain blood flow 36 percent, leaving cerebral oxygen consumption unaltered. The observed degree of cerebral vasodilatation represented the action of low  $P_{O_2}$ , unmodified by antagonistic effects of hypocapnea normally associated with hypoxia.

In studies carried out on dogs exposed to simulated altitudes of 25,000 feet for six hours daily, five times a week, for 1–27 months, Altland and Highman (594) 1956, found marked vascular engorgement in the heart. Changes in cardiac valves in other regions attributable to high altitudes were similar, but less frequent and less severe than in similarly exposed rats. Nine dogs with hematocrits from 67–81 (exposed 5–8 months) received bacteria (*Staphylococcus aureus*). Susceptibility to endocarditis under these experimental conditions was moderately increased in dogs exposed to simulated high altitudes.

Exposure of animals to high altitudes appears to increase the incidence of cardiovascular anomalies. Record and McKeown (615) 1955, found a high incidence of patent ductus arteriosus in guinea pigs examined 24–26 hours after birth. Baird (600) 1963, studied mice and rats at 12,470 feet. Among 33 Swiss albino mice, 23 sea level controls had no cardiovascular anomalies. In contrast 4 of 10 mice born and maintained on the mountain had congenital cardiovascular malformations, including interarterial and interventricular septal defects, patent foramen ovale, and persistent ductus arteriosus. All had postnatal anomalies, including right cardiac hypertrophy, hypervascularity and extreme atrial dilatation. Among the 62 Long-Evans rats, 26 sea level controls and 19 rats born at sea level, but transferred to the mountain, no congenital cardiovascular anomalies were seen. In contrast, 5 out of 17 rats conceived on the mountain had cardiovascular malformations, including dextrocardia with partial situs inversus, absent or extremely elongated innominate arteries, and

anomalous duplication of the basilar artery. Postnatal anomalies, including right cardiac hypertrophy, myocardial hypervascularity and hematocrits ranging to 71, were found among rats that had been on the mountain for prolonged periods, whether they were born at sea level or at high altitude. There was a definite correlation between continuous moderate hypoxia and the occurrence of congenital cardiovascular malformations and of postnatal cardiovascular anomalies in mice and rats. Similar findings have been reported by Baird and Cook (601) 1964.

Arias-Stella and Recavarren (592) 1962, studied 70 infants and children, born and living at sea level, and 59 similar subjects from high altitude (12,225-14,300 feet). The ratio of left and right ventricular weights (Hermann-Wilson Index) was measured in all of these subjects. It was shown that at sea level the Hermann-Wilson Index attained values corresponding to those characteristic of adults, beginning at the fourth month of life. In the high altitude group the ratio indicated a persistent right ventricular predominance. Normally present at birth, this ordinarily gives way in due course at sea level to left ventricular dominance. The apparent right ventricular hypertrophy in the high altitude group persisted from the fourth month of life up to the maximum age investigated (10 years). It was also observed that the degree of right ventricular predominance at birth and up to age three months was greater in infants born at high altitudes than at sea level. For further studies of cardiac anomalies in subjects born at high altitudes, a paper by Alzamora, Rotta, Battilana, Abugattas, Rubio, Bouroncle, Zapata, Santa-Maria, Binder, Subiria, Paredes, Pando and Graham (595) 1953, may be consulted.

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#### 4. BLOOD

It is well established that, with wide variations, exposure to reduced barometric pressure results in a polycythemic response. It appears that the response is directly proportional to the degree, duration, and continuity of the hypoxia, and that there is a limit beyond which the hypoxic stimulus will not cause an erythropoietic response. Extremely severe hypoxia may indeed cause a depression rather than further stimulation of the blood forming mechanisms. The immediate polycythemic response early in exposure to high altitude seems to be caused by release of stored blood, for example, from the spleen. Hyperactivity of the erythropoietic mechanism follows repeated or constant exposure to low pressures.

It may be that subjects living at high altitudes may not show significant differences in blood

values when compared and contrasted with persons living at low altitudes or at sea level. Such conclusions have been drawn by Sottano, Fernandez, Zangheri and Suarez (650) 1959. Blood values were determined in 30 men and 20 women between the ages of 18 and 27 living in Mendoza, Argentina (747 meters above sea level). The hemoglobin content was found in men to be 15.67 gm/100 ml; in women 13.48 gm/100 ml. The average number of erythrocytes in men was 5.449 million/mm<sup>3</sup>; and in women 4.697 million/mm<sup>3</sup>. For men the hematocrit values were 47.37 percent; and for women 43.17 percent. The average corpuscular hemoglobin content in men was 28.96  $\mu\text{g.}$ , and in women 29.56  $\mu\text{g.}$  The average corpuscular volume in men was 87.56  $\mu^3$ , and in women 91.5  $\mu^3$ . The average concentration of corpuscular hemoglobin in men was 33.08 percent and in women 32.01 percent. The authors reviewed 34 references to previous work and concluded that no significant differences in blood values were found between their subjects and those living at lower levels or at sea level. The differences between the values for men and for women were not significant. In a study of polycythemia of high altitudes, Reynafarje, Lozano and Valdivieso (646) 1959, observed that the degree of reticular cytolysis is closely related with changes in red cell iron turnover rate. There was an increase in human subjects examined of intestinal iron absorption during the early period of exposure to an altitude of 14,900 feet. After 48 hours of exposure this was estimated to be about three times higher than the absorption observed in subjects at sea level and in native residents at 14,900 feet. There was an increase of plasma and red cell iron turnover after two hours of arrival at 14,900 feet, indicating that the increase in the production of red cells to compensate for hypoxia is a very early response. The highest increase in plasma and red cell iron turnover rate took place between 7-14 days after exposure to high altitude. After six months of exposure there was still an elevated iron turnover rate. The native residents at 14,900 feet showed a red cell iron turnover rate of approximately 30 percent higher than healthy subjects at sea level. A progressive decrease in the plasma and red cell iron turnover rate was observed in native residents of high altitudes

when brought down to sea level, reaching a maximum after two to five weeks, and indicating a great degree of depression of red cell production. After that there was a gradual return to normal rates. Changes in the blood volume either during ascent or descent took place only after several weeks. The red cell mass variation occurring during the early periods of environmental change were compensated for by proportional changes in the plasma volume. The increase or decrease of the total blood volume after this period appeared to be due exclusively to red cell mass modification. Cytological studies of bone marrow carried out on subjects temporarily exposed or living permanently at high altitudes demonstrated a hyperplastic condition. The reverse, or an inhibition of red cell production took place when high altitude polycythemic subjects were brought down to sea level. This constitutes cytologic counter-proof for the iron turnover studies. The life span of the red blood cells after descent from high altitudes to sea level fell within normal patterns. However, it was not possible to determine whether there was an increased destruction of red cells during the first week. If there is a greater destruction, this would appear to be of a small degree affecting only the older elements. Mazzella (641) 1958, decompressed rabbits to 267 mm Hg (800 meters equivalent) for one hour and then returned them to sea level. Blood was collected before flight, immediately afterward, and subsequently 15 minutes, 30 minutes, 60 minutes and 120 minutes after flight. Hemoglobin, red blood corpuscles, platelets, white blood corpuscles, hematocrits, reticulocytes and mean corpuscular volume were found to be normal 15 minutes after return to sea level. There was some increase of hemoglobin, red blood count, hematocrit, platelets and reticulocytes. Similar findings were reported by Mazzella and Ghinozzi (642) 1958.

Reynafarje (645) 1957 found a general but close relationship between the degree of polycythemia and the level of altitude at which permanent residents live. These studies were carried out at Morococha, a mining town in the Andes, at an altitude of 4540 meters (14,900 feet), with a mean barometric pressure of 446 mm Hg. The native subjects showed a mean red cell count of 6,400,000 cells/mm<sup>3</sup>, and a hemoglobin

of 20 grams/100 ml of blood. The hematocrit was about 60 percent. It was found that the size and shape of circulating erythrocytes and the hemoglobin content did not differ essentially from the values found at sea level. Generally the total blood volume and red blood count increased in ten subjects taken to 14,900 feet and observed during one year of continuous residence. The opposite effect was found on three natives taken to sea level and studied during four months. In these latter subjects the blood volume and red blood count dropped. In subjects taken up to 14,900 feet the reticulocyte count reached a peak on the sixth day of a two week stay and dropping back by the end of the 14-day period almost to normal. This author's observations clearly showed that anoxic stimulus of high altitude environment causes an increase in red blood cell count in red blood cell precursors, but does not affect the granulocytes and the platelets. Hyperplasia of the erythropoietic tissue occurs at altitude and changing from high altitude to low altitude is characterized by an inhibition of the erythropoietic activity during the initial days of the new exposure. Working with rats, Contopoulos, Van Dyke, Simpson, Lawrence and Evans (629) 1954, found that suckling rats between the age of 4–16 days did not respond to hypoxia (15,000 feet equivalent for six hours) with an increased erythropoiesis as judged by increased hematocrit, hemoglobin and red blood corpuscular volume. Colehour (628) 1960, has conducted a study of erythropoietic stimulating factor production in pubescent mice after a single exposure to hypoxia. Pubescent, pre-pubescent, and post-pubescent mice were exposed for six hours to a simulated altitude of 22,000 feet, after which cardiac punctures were made on the first, second, third or fourth day for hematocrit and reticulocyte determinations. Baseline values were determined using similar animals without exposure to hypoxia. It was shown that mice after puberty have a reticulocyte response greater than baseline when subjected to a single hypoxic exposure, but do not have this capacity before puberty. Furthermore, if the production of erythropoietic stimulating factor (ESF) is accepted as the prerequisite to reticulocytosis it can be said that the endocrine changes at puberty are concomitant with the animals' ability



to increase the production of ESF. These studies may be correlated with the observation that pre-pubescent animals exhibit an increased binding capacity for oxygen by myoglobin.

Using  $C^{14}$  labelled glycine, Berlin, Reynafarje and Lawrence (625) 1954, found in Peruvians living at 12,000 feet that the red blood corpuscular life span varied between 109 and 117 days (average 114), and paralleled that of men at sea level. Similar results were found in rats by Fryers and Berlin (634) 1952. In animals acclimatized to high altitudes the life span of red blood cells was normal. Of the red cells produced during the initial phase of rapid erythropoiesis resulting from exposure of rats to simulated high altitude conditions, at least some showed a shorter than normal life span. Although not conclusive, the authors' evidence did not support the concept that increased destruction of red cells occurs on returning an altitude-acclimatized animal to sea level.

In a study of hemoglobin content in residents at high altitude, Rathe (644) 1959, determined values in 25 normal persons between 5 and 20 years of age, living at Mina Aguilar, Argentina (4515 meters altitude), and in Jujuy, Argentina (1270 meters altitude). No significant statistical differences were found in the hemoglobin content between the two groups. Dill (630) 1963, carried out a study during the summer of 1962 during the early phase of acclimatization to high altitude in six subjects who had participated in the previous expedition to the Chilean Andes in 1935. The ages of these subjects at the 1962 study ranged from 58–71. Two of the subjects had also taken part in a high altitude study in 1929. In 1935 the three on whom hemoglobin was determined beginning with their arrival at high altitude showed an immediate increase. A response in young men has been well established by other workers. In 1962 five of the six subjects exhibited a decrease in hemoglobin concentration during the first days. The greatest decrease was observed in the author who was the oldest subject. His hemoglobin was 88 percent of his sea level value after nine days at altitude and remained below his sea level value for another week. No observations were made on blood volume and hence the author could only speculate regarding the possible related responses. It seemed un-

likely to the author that there was unusual destruction of hemoglobin since none of the subjects engaged in strenuous exercise. Two hypotheses were advanced: 1) in this age range anoxia may slow up hematopoietic activity, or 2) there may be an early increase in total plasma volume that outruns the early increase, if any, in total red cell volume. Metcalfe, Meschia, Hellegers, Prystowsky, Huckabee and Barron (643) 1959, studied 36 ewes that had been born and raised at high altitudes and bred on known dates at the Institute of Andean Biology at 15,000 feet altitude. Samples of maternal arterial and uterine venous blood as well as fetal umbilical arterial and venous blood were taken anaerobically with the mother under spinal anesthesia. The data so obtained, when compared with findings at sea level, suggested a pattern of compensations both maternal and fetal to the alveolar hypoxia of altitude. There was a higher hemoglobin concentration, in both fetal and maternal blood, at high altitude. Despite this, the maternal arterial blood contained less oxygen due to its lower saturation. Uterine venous blood, however, contained more oxygen (at a slightly lower saturation) at high altitude than at sea level resulting in a decreased arteriovenous oxygen difference across the pregnant uterus, and a lower mean percentage saturation of maternal blood in the uterus. The umbilical venous blood, however, was as well saturated with oxygen by its passage through the uterus at high altitudes as at sea level.

In a study of the effects of high altitude upon the protein composition of human blood, Smolichev (649) 1961, determined the protein composition of the blood in 12 young healthy individuals in Stalinabad (850 meters) and during their stay in the mountains of East Pamir (4200 meters). During the first month of sojourn at high altitude the total concentration of protein was increased, while towards the end of the four-month period it dropped somewhat, but still remained above the initial level. The relative and absolute albumin content in the blood serum dropped immediately after the ascent and remained low for a month after descent from 4200 meters to 850 meters. The figures for ( $\alpha$ -1), B- and ( $\gamma$ -) globulin rose immediately after ascent. During the four-month stay at alti-

tude, the (alpha-1) and gamma globulins went back to normal. During the first month after descent figures for alpha-1, beta and gamma globulins were higher than the initial levels. The alpha-1 globulin went up only after descent. The oncotic pressure of blood rose during the first month after ascent and then returned to normal at the expense of increased concentration of the globulin fraction, which compensates for the decreased albumin content in blood serum. Trapani and Bartel (653) 1958, investigated the effect of high altitude on the electrophoretic distribution of plasma proteins in the rabbit. Sea level samples were obtained at the California Institute of Technology (755 feet) and the high altitude samples were collected at the Barcroft Laboratory, White Mountain Research Station, California (12,470 feet). During the first week of acclimatization there was a decrease in the percentage of albumin and an increase in the alpha and beta globulins. However, after an additional 30-day period the albumin was increased, and the alpha and beta globulins were decreased in relation to the sea level values. The gamma globulin did not change significantly during the exposure period. Total protein concentration increased approximately 30 percent after 37 days at altitude. Estimates of plasma volume based on the dilution of circulating antibodies give a value of approximately 30 percent less than plasma volumes measured in rabbits at sea level by the Evans Blue technique. The decrease in plasma volume and the increase in protein concentration indicate to the authors that the mass of circulating protein may not change, and in addition, the turnover rate did not appear to differ much from that in animals at sea level.

Exposure to high altitude results in a decrease of plasma potassium. Sussman, Pratt, Smith and Ferguson (652) 1953, decompressed Long-Evans male rats to a simulated altitude of 25,000 feet (282 mm Hg) and other rats to 30,000 feet (226 mm Hg) for 30 minutes and returned them to ground levels in 10–15 seconds. Controls were run with rats in the chamber at atmospheric conditions. Controls showed 6.23 mEq/liter; those at 25,000 feet showed 5.07 mEq/liter; and those at 30,000 feet showed 5.08 mEq/liter. The hematocrit was significantly elevated at 25,000

and 30,000 feet with no apparent difference between these two altitudes. Ferguson, Smith and Barry (632) 1956, subjected bilaterally adrenalectomized dogs maintained on cortisone or DCA, or in moderate adrenal insufficiency to a simulated altitude of 30,000 feet (225.6 mm Hg) for 90 minutes (three 30-minute periods). The plasma potassium concentration consistently showed a decrease by the end of the first 30-minute period and remained depressed for the duration of the decompression. This response was found to be statistically similar to that observed in intact dogs and indicated to the authors that, in this species, the hypokalemia of acute decompression stress is not mediated by the adrenal glands. As in intact dogs, the plasma sodium remained unchanged. In the adrenalectomized dogs, there was no increase in hematocrit. No eosinopenia was observed in intact dogs. Preliminary studies indicated that a respiratory alkalosis is associated with the plasma potassium changes occurring in dogs with decompression to 30,000 feet. Whether alkalosis is responsible for the potassium changes remains, according to the authors, to be determined. In subsequent reports Gold, Barry and Ferguson (635) 1959, (636) 1960, and (637) 1961, found that the potassium decrease at altitude in the dog in response to moderate altitude stress occurs without prior transient hyperkalemia, such as occurs in human subjects. It was also found that there was a temporal potassium-glucose relationship, the potassium decreasing and the glucose increasing simultaneously during exposure to altitude. It appears according to the authors that potassium ions leave the plasma and enter the tissue as a secondary response to alkalosis.

Weiner (655) 1959, exposed both young and mature rabbits in a decompression chamber to a simulated altitude of 6000 meters (64 mm Hg) for 45 days, and then returned them to normal atmospheric pressure and observed them for an additional period of 42 days. At altitude the serum transaminase level fell from 6 units to 3.4 units in 20 hours, and then rose to a value of 9.5 to 33 units for the remainder of the experiment, including the stay at normal pressure. Similarly, the adult animals showed an initial decline followed by a sharp increase in transaminase. Hemoglobin levels increased at altitude in both



the young and adult animals and decreased gradually at normal pressure. Lactic acid and pyruvic acid levels showed similar fluctuations, generally an initial rise followed by a decline and subsequent return to normal level. It appears that transaminase activity, which reflects the level of protein metabolism, is independent of the synthesis of hemoglobin. The lactic acid and pyruvic acid levels indicate the level of carbohydrate metabolism.

A study of the effect of decreased atmospheric pressure on blood volume of rats has been carried out by Fryers (633) 1952. The animals were exposed to an equivalent altitude of 15,000 feet for 3 to 100 days. Fully acclimatized rats were studied at 8,000 feet, 15,000 feet and 20,000 equivalent altitudes. A marked increase in total red cell volume and total hemoglobin was observed and it was reported that a steady state for hemoglobin and red cell volume at 15,000 feet was reached within ten days of lowering the barometric pressure. The total plasma volume was reduced to the same extent by exposure to altitudes of 15,000 feet and 20,000 feet. The rate of formation of new red cells was observed to be increased to 5.9 times normal during the development of acclimatization.

Carter (626) 1955, and Carter and Clark (627) 1958, have examined the effect in dogs of carbonic anhydrase inhibition during hypoxia. Trained unanesthetized dogs were acutely exposed to a barometric pressure of 350 mm. Hg in a decompression chamber. Diamox, the carbonic anhydrase inhibitor, was administered intravenously (100 mg/kg) before decompression in one series of runs and after decompression in another series. Arterial blood samples were analyzed for  $P_{O_2}$  by the Riley technique. Alveolar  $P_{CO_2}$  was estimated from end-tidal gas samples, while the arterial blood  $CO_2$  content was determined by the method of Van Slyke. Ventilation-gas exchange data were obtained on a recording spirometer. Decrease in arterial  $P_{O_2}$  following decompression was less in animals previously given Diamox than in controls. The arterial  $P_{O_2}$  rises when Diamox is given after steady state at altitude was obtained. Alveolar  $P_{CO_2}$  decreases more during ascent with Diamox than without Diamox. Alveolar  $P_{CO_2}$  decreases if Diamox is given after steady state at 350 mm.

Hg pressure. Diamox treated dogs manifested a higher ventilation equivalent for carbon dioxide when at 350 mm. Hg than controls at the same altitude. Diamox treated dogs manifested greater decrease in arterial carbon dioxide content after ascent than did control dogs, while no differences in expired air R.Q. were noted when treated dogs were compared to controls. All initial observations at altitude were made after at least 30 minutes of exposure, and all ground level observations represented the basal state.

Other enzyme studies include a report by Marra (640) 1960, who found in rabbits decompressed at about 130 meters per minute to a simulated altitude of 6700 meters for five hours, an increase in blood aldolase and ciruloplasmin levels, with no change in blood transaminase level. It was suggested by the author that modifications in blood enzymes are related to changes in the cellular permeability of muscles induced by hypoxic stress and its related metabolic changes.

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## 5. RESPIRATION

When one breathes ambient air at high altitudes a hypoxic stimulus causes a rapid increase in pulmonary ventilation. Pugh (678) 1957, (679) 1958, and Pugh, Gill, Lahiri, Milledge, Ward and West (680) 1964, have studied ventilation under conditions of high mountain exploration. Resting ventilation (BTPS) rose to 13-22 liters per minute (mean 15.8 liters per minute) above 18,000 feet, compared with 5.5-9.8 liters per minute (mean 7.3 liters per minute) at sea level. Ventilation at STPD was independent of altitude. Resistance hyperpnea on descending to lower altitude was not observed in the subjects studied and the reports of other members of the author's party on Mt. Everest suggested that individual responses to change of altitude were highly variable. Hall (666) 1951, and (667) 1952, has pointed out that the full effect on pulmonary ventilation of the hypoxic stimulus is counteracted by a concomitant hypocapnia. With the addition of carbon dioxide to the inspired air a more effective response to the hypoxic stimulus is manifested. The author concluded that while hypoxia and hypercapnia are separate stimulating factors and additive in their effects, the actual regulation of respiration at altitude appears to depend upon the manner of their interaction. Hornbein and Roos (670) 1961, have reported that hypoxia of mild degree ( $P_{A_{O_2}}$  above 60 mm. Hg) produces little or no



ventilatory response in resting man during the steady state. How respiratory acclimatization to altitudes below 10,000–12,000 feet can take place in the absence of a detectable hypoxic chemoreceptor drive has remained a mystery. It has been suggested that the mechanism initiating the process of acclimatization to mild hypoxia might differ basically from that at higher altitude where the ventilatory effect of chemoreceptor activity is apparent at rest. The possibility exists that the effectiveness of a hypoxic chemoreceptor drive might be enhanced by exercise. This was confirmed experimentally by the authors. These findings are confirmed by Dejours, Girard, Labrousse and Teillac (664) 1959, and Dejours, Labrousse, Raynaud, Girard and Teillac (665) 1958, in resting subjects.

For studies on respiratory adaptations to prolonged hypoxia, papers by Chiodi (660) 1956, (661) 1957, and (662) 1963, and by Astrand (658) 1954, should be consulted. The pulmonary ventilatory response to high altitude is higher in newcomers than in adapted residents.

Studies by Kreuzer (671) 1960; by Kreuzer, Tenney, Andersen, Schreiner, Nye, Mithoefer, Valtin and Naitove (672) 1960; and Kreuzer, Tenney, Mithoefer and Remers (673) 1962, on alveolar-arterial oxygen gradient should be consulted. These authors find in dogs and in man that the alveolar arterial oxygen gradient with air at altitude is lower than with air at sea level, and also lower than with 11 percent oxygen at sea level. The effect at altitude may be due to an increase of pulmonary diffusing capacity at altitude.

Of interest in connection with respiratory effects at high altitudes are studies during the past ten years or more on decompression treatment of whooping cough. The following authors may be consulted: Kriefer (674) 1953; Banks (659) 1955; Harnack (668) 1955; Verhoeven (683) 1957; and Heinonen and Karvonen (669) 1958. These reports cover the treatment of several hundred patients in which it appears that the treatment is inadequate for acutely ill patients, and that it is not effective or even better in the milder than in the more severe cases. Subjects are taken to an equivalent altitude of about 12,000 feet and maintained for 30 minutes to 45 minutes, three times a day, every

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## 6. ALIMENTARY TRACT

In general conditions of hypoxia decreased gastric motility can cause a delay in gastric emptying time in both animals and man. The gastrointestinal tract has been stated to be relatively resistant to hypoxia, as contrasted for example with the central nervous system. The propulsive motility of the small intestine is known to be decreased by hypoxia. The propulsive motility is significantly less in the unacclimatized than in the acclimatized animals. Gastric secretion tends to be diminished by hypoxia. According to Danhof and Steggerda (686) 1961, hyperventilation induced in human and animal subjects by simulated ascents to 15,000 feet altitude is accompanied by a lowering of blood  $PCO_2$  and a depression in gastric acid secretion presumably

as a result of interference with the role of carbon dioxide intracellularly. Naitoye and Tenney (687) 1960, studied gastric acid secretion in two normal human subjects at sea level and after one and six days of continuous residence at high altitude (14,246 feet). An evaluation of the separate and interacting effects of alveolar carbon dioxide and oxygen tensions on gastric acid secretion was made possibly by appropriate variations in the inspired mixtures. Exposure to the hypoxia and hypocapnia of high altitude resulted in a man increase in free HCl acid secretion to levels four times sea level controls. The same degree of hypocapnia at the higher  $PO_2$  at sea level resulted in a net decrease. After six days at altitude there was a fall in secretory rate towards normal. Hypercapnia was uniformly associated with marked increases in secretory levels, being highest at altitude. The findings suggested to the authors that the level of gastric acid secretion was directly related to alveolar  $PCO_2$  and that for any given  $PCO_2$ , secretion was inversely related to alveolar  $PO_2$ .

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## 7. METABOLISM

Cullumbine (690) 1952, has reported experiments in which male mice were exposed to a moderately low barometric pressure (460 mm. Hg) for a period of 48 hours. This exposure induced a preliminary involution of lymphoid tissue; increased weight, nitrogen and glycogen contents of the liver; reduced carcass fat and nitrogen; increased muscle glycogen; and reduced adrenal cholesterol content. Later there was a hypertrophy of the lymphoid tissue, reduced liver nitrogen and glycogen and a return of the carcass fat to near normal values. The carcass nitrogen continued to decrease, however, and the adrenal cholesterol remained at a low value. These responses were dependent on the presence of the pituitary gland and they were modified in various ways by removal of the adrenal glands, the thyroid and the testes. In order to ob-



tain a better understanding of the process associated with altitude acclimatizations, Green (693) 1961, subjected white rats to a simulated altitude of 18,000 feet in a low pressure chamber for several months. Groups of animals were sacrificed at regular intervals and various tissues analyzed for biochemical changes. GOT and GPT were reduced in both the liver and kidneys of the hypoxic animal. Cytochrome C reductase activity was reduced initially in both the liver and the kidney, but was higher than the control values after two months exposure, coinciding with the acclimatization. Succinic dehydrogenase was erratic in response to decreased oxygen tension, giving some insight into the contradictory results coming from different laboratories. Liver glycogen and blood glucose were consistently depressed in the hypoxic animals while heart glycogen was elevated during the early exposure, subsequently falling to a subnormal level. Heart-body ratios increased while other tissue ratios decreased. Total nucleotides were decreased in most tissues with heart and kidney being most resistant to change, respectively. It was concluded by the author that while many biochemical reactions are affected by hypoxia, the kidney seems to be most dramatically affected by acclimatization.

Terzioglu and Aykut (699) 1954, determined basal metabolic rates in 12 subjects (20–30 years of age) at various times during a stay of 12 days at an altitude of 1.85 km. The basal metabolic rate of each subject was found to be raised on the fifth and sixth days and remained that way until returned to sea level. The mean RQ dropped from 0.92 to 0.84 at altitude. Respiratory minute volume increased also, but tended to return to normal while the subject was still at altitude. Picon-Reategui (698) 1961, determined basal metabolic rate and body composition in 17 healthy adult male subjects living at an altitude of 14,900 feet above sea level. The BMR of high altitude residents fell within the limits considered normal for healthy adults at sea level. An increase in oxygen uptake in human beings at high altitude was observed by Grover (694) 1963. Multiple determinations of basal oxygen uptake were made on six individuals at both 5,200 feet and at 14,150 feet. The small but significant rise in oxygen uptake observed probably reflected,

according to the author, the energy required to increase ventilation. All of the subjects had lived at altitude for one year.

Growth rate may be reduced by long exposure to high altitude. Thus Valdivia, Richardson and Forbes (701) 1964, exposed pregnant guinea pigs to a simulated high altitude of 13,000 feet, the exposure starting between the 30th and 35th gestation days. Pregnant guinea pigs exposed to 13,000 feet delivered litters of normal size. The time of delivery was between the 60th and 70th days of gestation. The average weight of nine newborn males exposed to high altitude was  $71 \pm 4.8$  gm. and for eight females was  $73 \pm 6.4$  gm. The animals born at simulated high altitudes continued to be exposed at 13,000 feet. As the exposure continued their body weights remained significantly lower when compared to sea level animals of similar ages. The average body weight for guinea pigs 16 weeks of age reared in the laboratories was 800 grams in contrast with a weight of 600 grams for those reared in the low pressure chamber at a simulated high altitude of 13,000 feet.

The lactic acid content in human venous blood during hypoxia at high altitude has been studied by Harboe (695) 1957. Lactic acid concentration increased with the degree and duration of hypoxia. Apart from heights of 15,000 to approximately 20,000 feet, where lactic acid concentration increases simultaneously with increasing disability, such concentrations were poorly correlated with functional disability during hypoxia. Cain and Dunn (689) 1964, noted that blood lactic levels have been reported by some to be elevated during exposure to altitude and by others to be unaffected. After a three hour control period at ground level, unanesthetized dogs were exposed for eight hours at 21,000 feet simulated altitude (335 mm. Hg). Arterial lactic acid reached a peak value within the first two hours at altitude and gradually declined thereafter, and in most animals closely approached the control value during the eighth hour at altitude. Excess lactate changed in a similar manner. According to Lalli Venditti (697) 1959, there was an increase of lactic acid concentration in the brain of hypoxic rats which could be correlated with the duration of hypoxia and inversely correlated to the rate of ascent.

In studies of Fillios, Andrus and Naito (691) 1961, it was found that rats made polycythemic by prolonged exposure to simulated high altitudes also had a marked degree of coronary involvement, but no apparent increase in endocardial sudanophilia; whereas sea level cobalt polycythemia does not appear to favor an increase in coronary or endocardial sudanophilia. This suggests that polycythemia, per se, does not favor an increase in lipid deposition at these sites. These findings suggested to the authors that tissue hypoxia may account for the increase in coronary sudanophilia, while changes in endocardial sudanophilia appear to be related more closely to the circulating cholesterol for all the groups.

As to the effect of hypoxia upon succinic dehydrogenase activity of the heart, liver and skeletal muscles, Vacca (700) 1958, found in rats no noticeable changes at simulated altitudes of 8500-9000 meters (169-248 mm. Hg).

Whitehorn, Ullrick, Krone and Brennan (702) 1953, have reported on the influence of low oxygen tensions on the respiration of tissues of acclimatized rats. The purpose of the study was to determine whether tissues of acclimatized animals have increased ability to take and utilize oxygen at low tensions. Nine male albino rats were maintained at 18,000 feet simulated altitude for 10-15 weeks. Using a standard Warburg technique, respiratory rates of liver, ventricle, kidney and adrenal slices were compared to rates of tissues of five controls under concentrations of 100, 20 and 2 percent oxygen. It was found that the kidneys of acclimatized rats respired at a reduced rate under all three of the oxygen tensions, and that acclimatized adrenals showed higher than normal rates under all tensions. The respiration of liver and ventricle did not differ from control values. The acclimatized animals exhibited no changes in adrenal weight or total metabolism, but demonstrated cardiac hypertrophy and increased hemoglobin. These results confirmed previous experiments indicating increased adrenal and decreased kidney respiration in acclimatization. There is no indication that acclimatized tissues are better able to take up oxygen at low tensions than are tissues from unacclimatized animals.

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693. Green, J. A. Some biochemical changes in response to hypoxia. *Fed. Proc.*, 1961, 20: 210.

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698. Picón-Reátegui, E. Basal metabolic rate and body composition at high altitudes. *J. appl. Physiol.*, 1961, 16: 431-434.

699. Terzioglu, M. and R. Aykut. Variations in basal metabolic rate at 1.85 km altitude. *J. appl. Physiol.*, 1954, 7: 329-332.

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## 8. ENDOCRINES

Timiras, Batts, Hollinger, Karler, Krum and Pace (712) 1956, have studied endocrine responses during adaptation to moderately high altitude in rats. The weight and morphology of the adrenal glands, hypophysis, pancreas, testes and thyroid were investigated in these animals (P animals) exposed for various periods of time at the 12,500 foot level at the White Mountain Research Station, and in rats of the second generation born at the station (F<sub>2</sub> animals). These animals were compared with rats remaining in the parent colony on the Berkeley campus (sea level controls). Comparable conditions of food, caging and temperature were maintained. The P animals were born at sea level and maintained



at these levels for about ten weeks before transfer to White Mountain one and three days and two months before sacrifice. After one to three days of exposure, adrenal cortical activity was stimulated as indicated by 1) a 40–50 percent increase in adrenal weight, 2) a loss of adrenal ascorbic acid (after one day's exposure), and 3) a 60–80 percent decrease in the weight of the thymus, spleen and lymph nodes. No change in weight could be observed in the hypophysis, testes and thyroid. The preputial glands were significantly enlarged after three days exposure. After two months' exposure, the P animals exhibited a significant enlargement of the hypophysis and thyroid as well as of the adrenal, even when other criteria (such as growth, reproduction, blood hemoglobin and hematocrit) indicated adaptation to the new situation. Testes and preputial glands remained unchanged. On the other hand, in the F<sub>2</sub> animals born at high altitude, endocrine weights appeared to be similar to those of sea level controls.

Kline (708) 1952, has stated that exposure of cats to moderate and severe anoxia indicates involvement of the adrenal gland with an antagonistic action of medullary and cortical divisions. At 28,000 feet for 90 minutes the adrenal cortex exercises dominant control, as evidenced by decreases in plasma potassium concentration of 18 percent in normal cats, 19 percent in nephrectomized animals, and 14 percent in splanchnectomized cats. It is suggested that a 51 percent increase in urinary potassium and an 88 percent increase in volume indicate the action of cortin. When animals were acutely adrenalectomized, or adrenalectomized and nephrectomized, there was no decrease in plasma potassium with exposure to 28,000 feet. It was believed that increases of 58 percent and 69 percent in the plasma potassium concentration of normal and nephrectomized cats exposed to 40,000 feet were under the influence of the adrenal medulla, since similar increases were observed with the injection of adrenaline. When adrenalectomized and splanchnectomized cats were exposed to 40,000 feet the plasma potassium increased only 18 percent and 11 percent respectively. Pratt, Smith and Ferguson (711) 1955, found in 41 unanesthetized Wistar rats decompressed to simulated altitudes of 25,000, 28,000, 30,000 and 35,000 feet for 30 minutes, that

there was a significant reduction in plasma potassium concentration from the average value of 6.35 mEq/liter in 18 ground level control rats. In 20 unanesthetized, chronically adrenalectomized rats, maintained on 1 percent NaCl, there was no change in the plasma potassium concentration after decompression to a simulated altitude of 30,000 feet for 30 minutes. Injection of adrenaline (0.02 mg./100 gm.) into 14 adrenalectomized rats reduced the plasma potassium concentration by approximately the same amount as does moderate decompression in the intact rat. When either seven intact or two adrenalectomized rats were subjected to 40,000 feet (to the point of respiratory collapse), there was a significant increase in the plasma potassium concentration. Similar results were reported in dogs by Ferguson, Smith and Barry (707) 1957, and Barry, Ferguson, Gold and Smith (704) 1961. In the latter study the authors concluded that adrenal involvement appears to be a factor in the hypokalemia observed in restrained intact dogs subjected to simulated high altitude while in unrestrained dogs respiratory alkalosis seems to be solely responsible.

Urinary excretion rates of epinephrine and norepinephrine were measured in six men by Pace, Griswold and Grunbaum (710) 1964. After three days in Berkeley (100 meters), the subjects were taken to the Barcroft Laboratory of the White Mountain Research Station (3800 meters) where measurements were made for 24 days. Little change occurred in the epinephrine excretion rate, other than the expected diurnal variation. In contrast, norepinephrine excretion rate increased steadily, starting the second day at Barcroft, to twice that at sea level by the end of the 14 day sojourn (58.9 ug./24 hrs. compared with a mean sea level value of 30.8 ug./24 hrs.). Although the bulk of the increase occurred during the day, an increase was also noted in the overnight period. Mean resting heart rate rose from 69/minute at sea level to 92/minute by the second day at altitude, and then gradually fell to 87/minute by the 14th day. Neither norepinephrine excretion rate nor heart rate had returned to the original sea level value by the fourth day after the altitude sojourn. These data are interpreted by the authors as evidence for a substantial and continuing response of the sym-

pathetic nervous system during at least the first 14 days at altitude. They also indicate some measure of functional adaptation to increased norepinephrine.

The effects of hypoxia on fertility have been studied by Baird and Cook (703) 1961, who exposed Swiss albino rats continuously or discontinuously to simulated altitudes up to 25,000 feet or to 12 percent oxygen in nitrogen at sea level. All control matings were found to be fertile. Of 30 matings during continuous exposure to 14,200 or 18,000 feet, all were fertile. Of 36 matings during discontinuous exposure (6 hours/day) to 20,000 or to 25,000 feet, all resulted in impregnation. Of 28 matings during continuous exposure to 12 percent oxygen, only one gave negative results. In these mice aberrant reproductivity was manifested by gestational abnormalities, fetal and maternal deaths, congenital anomalies and cannibalism. Under the experimental conditions studied, fertility *per se* was adequate for the propagation of the species.

703. Baird, B. and S. F. Cook. Hypoxia and fertility in adapted mice. *Fed. Proc.*, 1961, 20: 210.

704. Barry, J. Q., F. P. Ferguson, A. J. Gold and D. C. Smith. Relation of respiratory alkalosis and adrenal activity to hypokalemia in restrained and unrestrained dogs subjected to simulated high altitude. *Fed. Proc.*, 1961, 20: 210.

705. Bruner, H., D. Jovy and K. E. Klein. Hypoxia as a stressor. *Aerospace Med.*, 1961, 32: 1009-1018.

706. DeBias, D. A. and K. E. Paschkis. Survival of adrenal-ectomized animals exposed to low barometric pressure. *Fed. Proc.*, 1960, 19: 154.

707. Ferguson, F. P., D. C. Smith and J. Q. Barry. Hypokalemia in adrenalectomized dogs during acute decompression stress. *Endocrinology*, 1957, 60: 761-767.

708. Kline, R. F. Role of adrenal glands in the plasma and urinary electrolyte changes during moderate and severe anoxia. *Fed. Proc.*, 1952, 11: 84.

709. Mefferd, R. B., Jr. Catecholamines in high altitude stress—a correlational analysis. *Fed. Proc.*, 1963, 22: 684.

710. Pace, N., R. L. Griswold and B. W. Grunbaum. Increase in urinary norepinephrine excretion during 14 days sojourn at 3,800 meters elevation. *Fed. Proc.*, 1964, 23: 521.

711. Pratt, A. J., D. C. Smith and F. P. Ferguson. Role of the adrenal gland in the response of plasma potassium of the rat to moderate and severe hypoxia. *Endocrinology*, 1955, 57: 450-455.

712. Timiras, P. S., A. A. Batts, G. W. Hollinger, R. Karler, A. A. Krum and N. Pace. Endocrine responses during adaptation to moderately high altitude. *Fed. Proc.*, 1956, 15: 187.

## 9. TEMPERATURE

Decompression to simulated 18,000 (380 mm. Hg) in a cool environment has been shown by Brown, Vawter and Marbarger (713) 1952, to produce significant changes in heart rate, systolic and diastolic blood pressure as compared to responses elicited during exposure to a cool environment uncomplicated by anoxia. Skin and rectal temperatures in these subjects were not significantly different during exposure to hypoxia in a cool environment, than those observed during exposure to the same environment in the presence of adequate oxygen. The response in human beings to exposure to a cool environment does not appear to be significantly altered by a reduced partial pressure of oxygen in the inspired air. Hale (714) 1953, in a series of observations on men exposed to hypoxia at high environmental temperatures, studied changes in circulation, respiration, body temperature and adrenal cortical function in male subjects during standardized exposures to low barometric pressure under two different conditions of temperature (80° and 120° F.). In preliminary tests, the elevation in heart rate resulting from 15 minutes exposure to 18,000 feet simulated altitude was slightly greater in 12 out of 19 subjects when they were in the overheated state. In the remaining seven, heart rate changes were elevated, but not to the degree seen when the temperature was in the comfort range. The elevation in heart rate due to the heat factor was apparent both before and after the hypoxia phase, but a truly 'additive' effect was not seen during hypoxia. Results from tests on a second group of subjects breathing a ten percent oxygen in nitrogen mixture show that time is an important element because there was a tendency for heart rates to decrease slightly after 15 minutes exposure to hypoxia at 80° F., but at higher temperatures heart rates either continued to climb throughout the exposure period or suddenly dropped to subnormal levels.

For a study of effects of thermal conditioning on metabolic response of rats to altitude, a paper by Mefferd and Hale (716) 1958, should be consulted. Hale and Mefferd (715) 1958, have also examined metabolic responses to thermal stresses of altitude acclimatized rats.



713. Brown, A. L., Jr., G. F. Vawter and J. P. Marbarger. Temperature changes in human subjects during exposure to lowered oxygen tension in a cool environment. *J. Aviat. Med.*, 1952, 23: 456-463.

714. Hale, H. B. Observations on men exposed to hypoxia at different environmental temperatures. *Fed. Proc.*, 1953, 12: 59.

715. Hale, H. B. and R. B. Mefferd, Jr. Studies on cross-adaptation; metabolic responses to thermal stressors of altitude-acclimated rats. USAF. Randolph AFB, Texas. School of Aviation Medicine. *Rept. no. 58-108*, September 1958, 6 pp.

716. Mefferd, R. B., Jr. and H. B. Hale. Studies on cross-adaptation; effects of thermal conditioning on metabolic responses of rats to altitude. USAF. Randolph AFB, Texas. School of Aviation Medicine, *Rept. no. 58-107*, September 1958, 5 pp.

## 10. KIDNEY

Renal function in men acclimatized to high altitude has been studied by Becker, Schilling and Harvey (717) 1957. These authors conducted their studies at the Andean Institute of Biology, Morococha, Peru (15,000 feet) on natives who for generations had been living at high altitude. These acclimatized persons represent a climatophysiological variety of the human race, different from sea level dwellers. The mean data on all subjects showed an 11 percent decrease in filtration rate, a 52 percent decrease in effective renal plasma flow, and an 89 percent increase in filtration fraction, with a 44 percent increase in hematocrit as compared to normal sea level values taken from the literature. In a study of 20 normal Peruvian men and women, natives at an altitude of 12,240 feet above sea level, Narvaes and Markley (722) 1957, found that plasma, sodium, and chloride were increased, plasma bicarbonate decreased and plasma potassium remained unchanged, as compared with corresponding values at sea level. In 18 natives of high altitude undergoing elective surgery for abdominal conditions, the postoperative response to surgical stress as measured by hematocrit, plasma and urinary electrolytes, as well as water and ion balance studies, were quite similar to the alterations reported at sea level in Peru and in other countries. All patients concerned withstood major abdominal surgery well and were discharged from the hospital symptomatically improved.

A number of studies have been carried out on the effects of hypoxia (decompression) on renal function in dogs. Marshall, Hanna and Specht

(721) 1952, found that intermittent exposure of dogs to progressively lowered barometric pressure approximately doubled the relative viscosity of the systemic blood when measured in capillary tubes. Effective renal plasma flow (PAH) rose slightly in three of the four dogs and changed little in the fourth. Since the plasma fraction of the blood was decreased (high hematocrit value) the calculated whole blood flow through the kidneys was approximately doubled. This was accomplished by vasodilatation which predominated in the afferent arterioles, as shown by a greater increase in glomerular filtration (creatinine), than in effective renal blood flow, so that the filtration fraction rose. Indirect evidence seemed to the authors to indicate that the changes depend solely on blood viscosity and not on renal tissue changes after adaptation has become adequate. This evidence consists of low early values for maximal tubular transfer of PAH which revert to normal as exposures are continued, statistically insignificant effects of altitude on PAH excretion at different saturation plasma levels, and simultaneous regression toward control levels of both circulatory and renal changes before the termination of exposures. Ferguson and Smith (718) 1953, and (719) 1953, studied the effects of hypoxia produced by decompression to a simulated altitude of 30,000 for 90 minutes in the case of unanesthetized dogs. Controls were subjected to all experimental manipulations except actual decompression. Particular attention was given to alterations in plasma electrolytes and renal function. Plasma potassium concentration consistently decreased (average about 19 percent) during the first 30 minutes of decompression, and remained at the low level throughout the rest of the period. Plasma sodium remained unchanged. Hematocrit values increased (average 5 percent) during the first 30 minutes and remained elevated throughout the rest of the decompression period. The significance of this effect was heightened by the fact that in the controls, hematocrit values decreased progressively with blood sampling. The eosinophil count showed a downward trend during decompression although the effect was not marked, however, blood samples taken 90 minutes after the animals had been returned to atmospheric pressure showed a significant de-

crease in eosinophiles. In the kidney, glomerular filtration rate showed no significant change during decompression, but urine flow decreased markedly in most experiments (average 44 percent), indicating an increased tubular reabsorption of water. Effects on sodium excretion were inconsistent, an increase being noted in about half of the experiments, a decrease, or no change, in the remainder. The data did not indicate to the authors that increased sodium excretion, when observed, was due to actual depression of tubular reabsorption of sodium. Potassium excretion consistently increased (average 30 percent) during decompression. Since this effect occurred simultaneously with decreased potassium filtration, it indicated to the authors a decreased tubular reabsorption and/or increased tubular secretion of potassium during decompression. Subsequent works by Ferguson and Smith (720) 1956, demonstrated that exposure of unanesthetized dogs to severe hypoxia (45,000-60,000 feet) until the onset of respiratory arrest, consistently produced a marked rise in plasma K concentration. In an attempt to determine whether the adrenal glands were essential for these responses, the experiments were repeated on bilaterally adrenalectomized dogs maintained on cortisone or DCA. In 17 experiments upon cortisone-maintained dogs, plasma K concentration decreased by an average of 19.7 percent during a 90 minute exposure to 30,000 feet. In 16 experiments on DCA-maintained dogs it decreased by an average of 15.5 percent under the same conditions. Urinary excretion of K increased during hypoxia in both series of experiments. Exposure of cortisone-maintained dogs to severe hypoxia resulted in an increase in plasma K concentration similar to that observed in intact animals under comparable conditions. These results appeared to the authors to support the conclusion that in dogs the presence of the adrenal gland was not essential for the changes in plasma and urinary K observed during acute decompression stress.

Effects of reducing atmospheric pressure on body water content have been studied by Picón-Reátegui, Fryers, Berlin and Lawrence (723) 1953, and by Siri, Reynafarje, Berlin and Lawrence (724) 1954, and Waterlow and Bunje

(725) 1958. In the studies of the first group of authors, on rats, water and weight loss were both maximal within the first week of exposure to a simulated altitude of 15,000 feet. Loss of water accounts for 94 percent of the reduction in weight observed during the first six days of exposure of rats to reduced atmospheric pressure at this level.

717. Becker, E. L., J. A. Schilling and R. B. Harvey. Renal function in man acclimatized to high altitude. *J. appl. Physiol.*, 1957, 10: 79-80.

718. Ferguson, F. P. and D. C. Smith. Effects of acute decompression stress upon plasma electrolytes and renal function in dogs. *Amer. J. Physiol.*, 1953, 173: 503-510.

719. Ferguson, F. P. and D. C. Smith. Effects of severe hypoxia upon plasma electrolytes and renal function in dogs. *Fed. Proc.*, 1953, 12: 42.

720. Ferguson, F. P. and D. C. Smith. Effects of acute decompression stress upon plasma and urinary potassium in adrenalectomized dogs. *Fed. Proc.*, 1956, 15: 62.

721. Marshall, L. H., C. H. Hanna and H. Specht. Renal function in the dog during increased blood viscosity produced by simulated altitude exposure. *Amer. J. Physiol.*, 1952, 171: 499-506.

722. Narvaes, E. and K. Markley. Postoperative water and electrolyte changes in natives of high altitudes. *J. appl. Physiol.*, 1957, 10: 383-387.

723. Picon-Reátegui, E., G. R. Fryers, N. I. Berlin and J. H. Lawrence. Effect of reducing the atmospheric pressure on body water content of rats. *Amer. J. Physiol.*, 1953, 172: 33-36.

724. Siri, W. E., C. Reynafarje, N. I. Berlin and J. H. Lawrence. Body water at sea level and at altitude. *J. appl. Physiol.*, 1954, 7: 333-334.

725. Waterlow, J. C. and H. W. Bunje. Electrolyte changes during acclimatization to high altitude; observations made on the British Expedition to the Colombian Andes, January, 1957. USAF, Randolph Air Force Base, Texas. School of Aviation Medicine. *Rept. no. 58-79*, August, 1958, 15 pp.

## 11. TOLERANCE

For general papers on tolerance the reader is referred to reports by Balke (726) 1963, Balke and Wells (727) 1958, Darling (731) 1959, and Parsons (740) 1958. Pugh has reported that above 23,000 feet without oxygen there occurs paralysis, loss of vision and euphoria preceding loss of consciousness. Prolonged exposure (two hours) at this level is fatal. Mood changes are similar to alcohol intoxication. Memory and intelligence are affected between 12,000 and 18,000 feet. The auditory system is less sensitive to



hypoxia than is the visual system. The accepted limit of arterial oxygen saturation for normal mental function is 85 percent (10,000 feet breathing air, or 33,000 feet breathing oxygen). For consciousness it is 55–60 percent (five to seven minutes at 25,000 feet or two minutes at 30,000 feet). Chronic exposure to altitudes between 20,000 and 23,000 result in insomnia, anorexia and weakness. Mental work is slow but efficient. Above 25,000 feet there is impairment of judgment and insight and of ability to initiate thought or action, although once a task is begun it is usually completed. Use of oxygen above 20,000 feet prevents symptoms. Full recovery from fatigue at extreme altitude takes days or weeks after descent. There is apparently little aftereffect of chronic exposure, but occasionally persistent impairment of memory may be a symptom. Ilk, Seguin, Bhatia and Stevenson (736) 1961, have used cessation of abdominal contractions in unanesthetized rats decompressed to 40,000 feet, as the end point for tolerance with survival to decompression hypoxia. Using this end point it was found that tolerance to altitude was decreased by acute exposure to severe heat or repeated restraint before decompression, and was increased by acute exposure to heat and then cold. Altitude tolerance was not affected by prior intermittent exposure to severe cold, but was reduced by intermittent exposure to severe heat or by decompression in a relatively dry environment. A pentobarbital anesthesia inhibited gasping and abdominal contractions and appeared to reduce altitude tolerance.

Young adult male and female Sprague-Dawley rats were exposed by Bartlett and Altland (728) 1959, to a simulated altitude of 33,500 feet, both with and without restraint. The exposure was begun immediately upon the restraint of the experimental animals. The restrained animals died significantly sooner than did the nonrestrained controls. Bartlett and Phillips (729) 1960, in a study of restraint adaptation and altitude tolerance in the rats used 64 adult, male, albino, Wistar rats, divided equally into two groups. Members of one group were subjected to the stress of light restraint for one week to produce adaptation to this stress. The other group was not restrained and served as controls. For altitude tolerance studies both groups were fur-

ther divided into restrained and nonrestrained animals which were simultaneously exposed to an altitude of 33,500 feet. Both the restrained and nonrestrained animals showed significantly longer survival times than the corresponding nonadapted rats. Restraint adaptation, however, did not prevent the earlier deaths of the restrained as compared to the nonrestrained animals.

A paper by Sobel, Sideman and Arce (746) 1960, serves as an example of a study of effects of hormone on tolerance. These authors found a mortality of 37 percent in guinea pigs decompressed to a simulated altitude of 25,000 feet for six hours. Morphine sulfate in doses of 2.5 mg. or 5 mg./100 gm. of body weight, increased the mortality to 50 and 70 percent respectively. Prior treatment with cortisone for three days reduced the mortality to 22 and 29 percent respectively. Multiple injections with ACTH reduced mortality to 19 percent.

The anorectic responses to radiation and their effect upon altitude tolerance have been reported by Newsom and Kimeldorf (739) 1956. Food consumption of rats, rabbits, mice, guinea pigs and hamsters was measured for three days following an approximately mid-lethal dose of x-irradiation to assess the degree of postirradiation anorexia. Seventy-two hours after irradiation these animals, as well as *ad libitum* fed and food deprived (72 hours) nonirradiated animals, were exposed to an altitude tolerance test. The mortality produced was used as the criterion of altitude tolerance. The altitude exposure selected for these species was sufficient to produce a mortality response of 50 percent or greater in nonirradiated animals during four hours of exposure. Irradiated rabbits and rats exhibited a severe decrease in food consumption which persisted for the three days of observation. Irradiated rabbits had an increased altitude tolerance similar to that previously observed by the authors in the rat. When nonirradiated rabbits were deprived of food for 72 hours prior to altitude exposure, the altitude tolerance was similar to that of the irradiated animal. While the food consumption was lower during the three days following irradiation in mice, the effect was much smaller than that observed for rats and rabbits. Guinea pigs and hamsters exhibited only a slight decrease in food consumption with recovery oc-

curing after 24 hours. The mice, guinea pigs and hamsters did not exhibit an increase in altitude tolerance three days after irradiation. However, when nonirradiated mice and guinea pigs were food deprived, the altitude tolerance was significantly increased. These observations provide further evidence that the post-irradiation increase in altitude tolerance is dependent upon the post-irradiation anorexia. The character of the diet affects tolerance to altitude hypoxia as shown in the mouse by Hershgold and Riley (734) 1959. It has previously been shown that mice with alimentary lipemia had a diminished survival time at altitude compared with controls fed isocaloric amounts of starch. These results were believed by the authors to provide evidence of a relative hypoxia associated with lipemia. In the authors' study 230 mice were brought to a simulated altitude of 33,000 feet and showed survival times distributed into three groups depending on the food given them four hours prior to exposure. Animals which were fasting (20 hours previously), or which had been fed coconut, olive or corn oils had survival times of about  $56 \pm 20$  seconds. Those given a normal diet, or one with added olive oil or protein survived an average of  $110 \pm 49$  seconds. Mice fed a starch-sucrose, or sucrose solution isocaloric with the lipids, lived about  $320 \pm 162$  seconds. The differences were found to be statistically significant ( $p < .01$ ). These studies show a salutary influence of carbohydrates on oxygen utilization at altitude. This effect was present when carbohydrate was given alone, or with either fat or the normal diet. Fat added to a normal diet failed to decrease resistance. Since there was no difference in tolerance between the fat-fed mice and the fasting mice, it was felt by the authors that lipids are not themselves detrimental, but rather are unable to provide the protection conferred by carbohydrates.

In both man (Dill, Robinson, Balke and Newton (732) 1964) and in animals (rats) (Flückiger and Verzar (733) 1955), tolerance to altitude hypoxia decreases with age. A species difference may also be discerned as shown by Cook and Leon (730) 1960. These authors showed that squirrel monkeys had a lower tolerance than C-57 mice.

Tolerance to acute hypoxia in man has been shown by Velasquez (747) 1959, to be higher in subjects born and living at high altitudes, than at sea level. Native residents living at an altitude of 14,900 feet were suddenly exposed to simulated higher altitudes ranging from 30,000–40,000 feet in a low pressure chamber. The 'time of consciousness' and the ceiling breathing air were determined. Comparing the results with those given by other investigators using sea level residents the author concluded that a man born and residing at an altitude of 14,900 feet has a definitely greater tolerance to acute hypoxia than a man born and living at sea level.

726. Balke, B. Human tolerances. pp. 149–171 in: *Physiology of man in space*. Edited by J. H. U. Brown, Academic Press Inc., New York, 1963, 348 pp.

727. Balke, B. and J. G. Wells. Ceiling altitude tolerance following physical training and acclimatization. *J. Aviat. Med.*, 1958, 29: 40–47.

728. Bartlett, R. G., Jr. and P. D. Altland. Effect of restraint on altitude tolerance in the rat. *J. appl. Physiol.*, 1959, 14: 395–396.

729. Bartlett, R. G., Jr. and N. E. Phillips. Restraint adaptation and altitude tolerance in the rat. *J. appl. Physiol.*, 1960, 15: 921–924.

730. Cook, S. F. and H. A. Leon. Survival of C-57 mice and squirrel monkeys in high and low pressures of oxygen. USAF. Holloman Air Force Base, New Mexico. Air Force Missile Development Center. *Project 6892, Rept. no. AFMDC-TR-60-21*, October 1960, 34 pp.

731. Darling, R. C. High altitude sickness, pp. 480–483 in: *A textbook of medicine*. Edited by R. L. Cecil and R. F. Loeb, W. B. Saunders Co., Philadelphia, 1959, 1665 pp.

732. Dill, D. B., S. Robinson, B. Balke and J. L. Newton. Work tolerance: age and altitude. *J. appl. Physiol.*, 1964, 19: 483–488.

733. Flückiger, E. and F. Verzar. Lack of adaptation to low oxygen pressure in aged animals. *J. Gerontol.*, 1955, 10: 306–311.

734. Hershgold, E. J. and M. B. Riley. Diet induced variations in tolerance to altitude hypoxia in the mouse. *Fed. Proc.*, 1959, 18: 68.

735. Hock, R. J. Translocation in altitude and endurance running of deer mice. *Fed. Proc.*, 1964, 23: 522.

736. Ilk, S. G., J. J. Seguin, B. Bhatia and J. A. F. Stevenson. A criterion to assess the effect of various factors on altitude tolerance. *Fed. Proc.*, 1961, 20: 211.

737. Luft, U. C. Altitude sickness. pp. 120–142 in: *Aerospace medicine*. Edited by H. G. Armstrong, Williams and Wilkins Co., Baltimore, 1961, 633 pp.

738. Matthews, B. Limiting factors at high altitude. *Proc. roy Soc.*, 1954, 143: 1–4.

739. Newsome, B. D. and D. J. Kimeldorf. Anorectic responses to radiation and their effect upon altitude tolerance. *Fed. Proc.*, 1956, 15: 136.



740. Parsons, V. A brief review of aviator's decompression sickness and the high altitude selection test. *J. R. nav. med. Serv.*, 1958, 44: 2-13.

741. Pugh, L. G. C. E. The effect of acute and chronic exposure to low oxygen supply on consciousness. pp. 106-116 in: *Environmental effects on consciousness*. Edited by Karl E. Schaefer. The MacMillan Company, New York, 1962, 146 pp.

742. Reed, D. J. and R. H. Kellogg. Effect of sleep on hypoxic stimulation of breathing at sea level and altitude. *J. appl. Physiol.*, 1960, 15: 1130-1134.

743. Scano, A. Alcuni effetti dell'intemperanza e del riposo insufficiente sulla resistenza alla depressione barometrica. *Riv. Med. aero.*, 1958, 21: 63-67.

744. Schilling, J. A., R. B. Harvey, E. L. Becker, T. Velásquez, G. Wells and B. Balke. Work performance at altitude after adaptation in man and dog. *J. appl. Physiol.*, 1955-56, 8: 381-387.

745. Shephard, R. J. Physiological changes and psychomotor performance during acute hypoxia. *J. appl. Physiol.*, 1956, 9: 343-351.

746. Sobel, H., M. Sideman and R. Arce. Effect of cortisone on survival of morphine treated guinea pigs under decompression hypoxia. *Proc. Soc. exp. Biol., N.Y.*, 1960, 104: 31-32.

747. Velásquez, T. Tolerance to acute anoxia in high altitude natives. *J. appl. Physiol.*, 1959, 14: 357-362.

## 12. ACCLIMATIZATION

The functional adaptations underlying acclimatization are highly complex and involve changes in cardiovascular and respiratory systems, as well as alterations in neurological, hematological and other functions. For general studies of acclimatization the reader is referred to papers by Clark, Bancroft and Hale (751) 1960; Hurtado (755) 1960; Hurtado (756) 1963; Hurtado and Clark (757) 1960; Hurtado, Velasquez, Reynafarje, Lozano, Chavez, Salazar, Reynafarje, Sanchez and Muñoz (758) 1956; Lalli (762) 1958; Lambertsen (763) 1961; Lambertsen (764) 1961; Lawrence, Huff, Siri, Wasserman and Hennessy (765) 1952; Specht (772) 1958; and Ward (779) 1954. Studies of tissue changes accompanying acclimatization to low atmospheric oxygen have been carried out by Duckworth (752) 1961; Tappan, Potter, Reynafarje and Hurtado (733) 1956; Tappan and Reynafarje (774) 1956; Tappan and Reynafarje (775) 1957; Tappan, Reynafarje, Potter and Hurtado (776) 1957; and Ullrick, Whitehorn, Brennan and Krone (777) 1956. For studies on brain metabolism during acclimatization at high altitude a paper by Albaum and Chinn (748) 1953, may be consulted. Sever-

inghaus, Mitchell, Richardson and Singer (770) 1963, have made measurements of CSF pH in human subjects during acclimatization. Excretion of urinary steroids at sea level and high altitude have been studied by San Martin, Prato and Fernandez (769) 1956; and acclimatization and deacclimatization changes in bone marrow volume and cellularity have been studied by Gong (753) 1963. For a paper on the effects of altitude acclimatization on work capacity, a report of Balke, Wells and Ellis (749) 1956, should be consulted.

748. Albaum, H. G. and H. I. Chinn. Brain metabolism during acclimatization to high altitude. *Amer. J. Physiol.*, 1953, 174: 141-145.

749. Balke, B., J. G. Wells and J. P. Ellis. Effects of altitude acclimatization on work capacity. *Fed. Proc.*, 1956, 15: 7.

750. Bourdillon, T. D. The use of oxygen apparatus by acclimatized men. *Proc. roy. Soc.*, 1954, 143: 24-32.

751. Clark, R. T., R. W. Bancroft and H. B. Hale. Aviation medicine. pp. 43-48 in: *Medical physics*. O. Glasser, Editor. Year Book Press, Chicago, 1960, 754 pp.

752. Duckworth, M. W. Tissue changes accompanying acclimatization to low atmospheric oxygen in the rat. *J. Physiol.*, 1961, 156: 603-610.

753. Gong, J. K. Acclimatization and deacclimatization changes in marrow volume and cellularity in dogs. *Fed. Proc.*, 1963, 22: 684.

754. Gray, E. LeB. Appetite and acclimatization to high altitude. *Milit. Med.*, 1955, 117: 427-431.

755. Hurtado, A. Some clinical aspects of life at high altitude. *Ann. intern. Med.*, 1960, 53: 247-258.

756. Hurtado, A. Natural acclimatization to high altitudes. pp. 71-82 in: *The regulation of human respiration*. Edited by D. J. C. Cunningham and B. B. Lloyd. Blackwell Scientific Publications, Oxford, 1963, 591 pp.

757. Hurtado, A. and R. J. Clark. Parameters of human adaptation to altitude. pp. 352-369 in: *Physics and medicine of the atmosphere and space*. Edited by O. O. Benson and H. Strughold. John Wiley and Sons, New York, 1960, 645 pp.

758. Hurtado, A., T. Velásquez, C. Reynafarje, R. Lozano, R. Chavez, H. A. Salazar, B. Reynafarje, C. Sanchez and J. Muñoz. Mechanisms of natural acclimatization. Studies on the native resident of Morococha, Peru at an altitude of 14,900 feet. USAF, Randolph AFB, Texas. School of Aviation Medicine. *Rept. no. 56-1*, March 1956, 62 pp.

759. Kellogg, R. H., N. Pace, E. R. Archibald and B. E. Vaughan. Respiratory response to inspired CO<sub>2</sub> during acclimatization to altitude. *Fed. Proc.*, 1956, 15: 108.

760. Kellogg, R. H., N. Pace, E. R. Archibald and B. E. Vaughan. Respiratory response to inspired CO<sub>2</sub> during acclimatization to an altitude of 12,470 feet. *J. appl. Physiol.*, 1957, 11: 65-71.

761. Kellogg, R. H., B. E. Vaughan and D. W. Badger. Respiratory responses to acute changes in O<sub>2</sub> and CO<sub>2</sub> during acclimatization to high altitude. *Fed. Proc.*, 1957, 16: 70.

762. Lalli, G. I meccanismi chimici tissulari nell'acclimatazione alle quote elevate. *Riv. Med. aero.*, 1958, 21: 119-136.

763. Lambertsen, C. J. Anoxia, altitude, and acclimatization. Altitude and aviation. pp. 699-705 in: *Medical physiology*. Edited by P. Bard. C. V. Mosby Company, St. Louis, 1961, 1339 pp.

764. Lambertsen, C. J. Anoxia, altitude, and acclimatization. Acclimatization. pp. 705-709 in: *Medical physiology*. Edited by P. Bard. C. V. Mosby Company, St. Louis, 1961, 1339 pp.

765. Lawrence, J. H., R. L. Huff, W. Siri, L. R. Wasserman and T. G. Hennessy. A physiological study in the Peruvian Andes. *Acta med. scand.*, 1952, 142: 117-131.

766. Michel, C. C. and J. S. Milledge. Respiratory regulation in man during acclimatization to high altitude. *J. Physiol.*, 1963, 168: 631-643.

767. Push, L. G. C. E. The effects of oxygen on acclimatized men at high altitude. *Proc. roy. Soc.*, 1954, 143: 14-17.

768. Riley, R. L., A. B. Otis and C. S. Houston. Respiratory features of acclimatization to altitude. pp. 143-157 in: *Handbook of respiratory physiology*. Edited by W. M. Boothby. USAF, Randolph AFB, Texas, School of Aviation Medicine, September 1954, 189 pp.

769. San Martín, M., Y. Prato and L. Fernandez. Mechanisms of natural acclimatization; excretion of urinary steroids at sea level and at high altitudes. USAF, Randolph AFB, Texas. School of Aviation Medicine. *Rept. no. 55-100*, August 1956, 2 pp.

770. Severinghaus, J. W., R. A. Mitchell, B. Richardson and M. M. Singer. CSF pH in man during acclimatization to high altitude. *Fed. Proc.*, 1963, 22: 223.

771. Skrypin, V. A. Znachenie ugol'noi kisloty pri kislorodnom golodanii organizma. The significance of carbon dioxide in anoxia. *Vo-med. Zh.*, 1960, 1: 65-71. *Milit. med. J.*, 1960, 1: 104-113.

772. Specht, H. Effects of maintained low atmospheric pressure. pp. 611-619 in: *Industrial hygiene and toxicology*. Volume I. Edited by F. A. Patty, Interscience Publishers, Inc., New York, 1958, 830 pp.

773. Tappan, D. V., V. R. Potter, B. Reynafarje and A. Hurtado. Mechanisms of natural acclimatization; tissue enzyme studies and metabolic constituents in altitude adaptation. USAF, Randolph AFB, Texas. School of Aviation Medicine, *Rept. no. 55-98*, October 1956, 13 pp.

774. Tappan, D. V. and B. Reynafarje. Mechanisms of natural acclimatization; tissue pigment studies in altitude adaptation. USAF, Randolph AFB, Texas. School of Aviation Medicine, *Rept. no. 56-97*, October 1956, 8 pp.

775. Tappan, D. V. and B. Reynafarje. Tissue pigment manifestations of adaptation to high altitudes. *Amer. J. Physiol.*, 1957, 190: 99-103.

776. Tappan, D. V., B. Reynafarje, V. R. Potter and A. Hurtado. Alterations in enzymes and metabolites resulting from adaptation to low oxygen tensions. *Amer. J. Physiol.*, 1957, 190: 93-98.

777. Ullrick, W. C., W. V. Whitehorn, B. B. Brennan and J. G. Krone. Tissue respiration of rats acclimatized to low barometric pressure. *J. appl. Physiol.*, 1956, 9: 49-52.

778. Valdivia, E. Mechanisms of natural acclimatization; capillary studies at high altitudes. USAF, Randolph AFB, School of Aviation Medicine, *Rept. no. 55-101*, June 1956, 6 pp.

779. Ward, M. High altitude deterioration. *Proc. roy. Soc.*, 1954, 143: 40-42.

### 13. PATHOLOGY

The extent and severity of pathological lesions in both man and animals attributable to high altitude hypoxia depend upon the duration of exposure, the severity of hypoxia and the repetitive character of the exposure. There is an organ and system specificity, the central nervous system being most susceptible. The following references represent a small selection of the literature on this subject: Hurtado (782) 1955; Metz (784) 1951; Brooks and Reeves (781) 1960; Talbot (785) 1960; Altland and Highman (780) 1960; Valdivia (786) 1961; and Innes and Saunders (783) 1962.

780. Altland, P. D. and B. Highman. Effects of high altitude on cholesterol-fed rabbits: Production of severe pulmonary atherosclerosis with calcification. *Arch. Path.*, 1960, 70: 349-357.

781. Brooks, R. A. and J. L. Reeves. Influence of intermittent exposure to simulated altitude on organ histology in rats. USAF, Brooks AFB, Texas. School of Aviation Medicine. *Rept. no. 60-81*, September 1960, 8 pp.

782. Hurtado, A. Pathological aspects of life at high altitude. *Milit. Med.*, 1955, 117: 272-284.

783. Innes, J. R. M. and L. Z. Saunders. Experimental lesions produced by anoxia (decompression chamber) and by carbon monoxide. pp. 78-80 in: *Comparative neuropathology*. Academic Press, New York, 1962, 839 pp.

784. Metz, B. Comparative experimental studies of the effects of simulated high altitudes on five vertebrates. *J. Aviat. Med.*, 1951, 22: 132-136.

785. Talbot, J. H. Altitude: pathologic effects. pp. 14-16 in: *Medical physics*. Vol. III. O. Glasser, Editor. Year Book Publishers, Chicago, 1960, 754 pp.

786. Valdivia, E. Histochemical demonstration of tissue adaptation to chronic hypoxia. *Fed. Proc.*, 1961, 20: 209.



#### IV. PHYSIOLOGICAL EFFECTS OF HIGH CARBON DIOXIDE CONTENT IN ENVIRONMENTAL AIR

##### A. GENERAL STUDIES

Although the acute and sub-acute effects of increased carbon dioxide content in the respired air has been thoroughly investigated in man as well as animals, nevertheless there are still inadequacies in our comprehension of the action of high concentrations of carbon dioxide over prolonged time periods. Our lack of this knowledge is no longer as critical so far as submarine operations are concerned. This is primarily because the modern nuclear boats are equipped with scrubber systems which hold the carbon dioxide concentrations within limits that are tolerable for even extended operations. In hard hat diving the ventilation is adequate, or more than adequate, to obviate carbon dioxide problems. But in the design of SCUBA equipment in which technical progress is constantly being made, the question of carbon dioxide accumulation must always be considered as a design and physiological problem. Moreover, in pressure chamber operations one has always to be constantly on guard against intolerable levels of carbon dioxide. For example, the chamber must be adequately ventilated, and/or the chamber atmosphere continuously scrubbed.

The papers listed in the present section provide an overall view of the carbon dioxide problem as a whole. Special mention may be made of the National Research Council Committee report on Underwater Physiology (800) 1956, pointing out that in general carbon dioxide inhalation produces respiratory stimulation, cerebral dilatation, and headache, and if the carbon dioxide concentration is above ten percent at sea level, there is confusion leading to unconsciousness. Concentrations of 20-30 percent result in myoclonic twitchings and convulsions. Cerebral blood flow increases when the carbon dioxide is above two percent. Increase of carbon dioxide tension to levels above 50 mm. Hg will decrease oxygen tolerance. White (801) 1954, has also dealt in general with the acute toxicity of carbon dioxide. This paper is useful as a review of older reports. Major difficulty may be expected to be encountered when the inhaled carbon diox-

ide ranges from four to seven percent, that is to say when the physiological equivalent of inhaled  $p\text{CO}_2$  approaches the alveolar  $p\text{CO}_2$ . Unconsciousness has been reported in 3 out of 31 subjects when 10.4 percent carbon dioxide was used and 2 out of 41 human subjects with 7.6 percent carbon dioxide.

787. Altman, P. L., J. F. Gibson, Jr. and C. C. Wang. *Handbook of respiration*. Edited by D. S. Dittmer and R. M. Grebe. W. B. Saunders Co., Philadelphia, 1958, 403 pp.

788. Alvis, H. J. Man, submarines and carbon dioxide. *Arch. industr. Hyg.*, 1952, 5: 344-346.

789. Goddard, D. R. The biological role of carbon dioxide. *Anesthesiology*, 1960, 21: 587-596.

790. Lambertsen, C. J. Neurological control of respiration. pp. 613-632 in: *Medical physiology*. Edited by P. Bard. C. V. Mosby Company, St. Louis, 1961, 1339 pp.

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## B. NERVOUS SYSTEM

For a general paper on the effects of carbon dioxide on nervous system function, the reader is referred to Schaefer (860) 1962. Acute exposure to carbon dioxide in human subjects for 15 minutes (7.5 percent proving minimum for generalized symptoms) results in various combinations of dyspnea and headaches, vertigo, sweating and numbness, over-activity of limbs, increased motor activity and restlessness, visual and color distortions, loss of balance and mental disorientation. Exposure of human subjects for three to six days in three percent carbon dioxide results during the first 24 hours in general excitation associated with a drive for increased activity as well as euphoria. During the second day there is a feeling comparable to a hangover, together with dullness and volatile changes of mood. During the second and third day memory and attentiveness are decreased and during the following day a restless sleep. A slight improvement occurs after the third day. Equivalent effects are seen in guinea pigs subjected to three percent carbon dioxide and more striking effects in animals breathing 12 percent carbon dioxide. Performance tests in man reveal an increased error production. Nerve excitation time chronaxie and the rheobase were decreased during the first day and a half and increased to twice their original value from the third day on. The biphasic response corresponded to a period of uncompensated respiratory acidosis followed by a period of compensation. Carbon dioxide accumulation during prolonged submerged operations in submarines showed similar effects with adaptation after two weeks except for aberrations in thinking processes and altered mental alertness. Subjects with normally slow respiratory rates and large tidal volumes exhibited increased tolerance to hypercapnia as well as to hypoxia. The mechanism of carbon dioxide action was examined in eight waking monkeys exposed to 10–30 percent carbon dioxide. Spontaneous electrical activity in the cortex after ten minutes exposure to carbon dioxide showed a decrease in amplitude of background activity and reduction of high voltage bursts. In the hypothalamus, within five minutes of exposure the three to five cycles per second (cps)

activity increased in amplitude forming regular three to five cps waves of 75 microvolts and persisted for one to two minutes after changing to air. Carbonic anhydrase activity and sodium content fell significantly in the hypothalamic region and increased with slight fall in potassium in cortical areas in guinea pigs exposed to 15 percent carbon dioxide for seven days. Histopathologically, according to the author, carbon dioxide is a specific rather than an anoxic agent.

For studies on the physiological action of carbon dioxide on the cortex and hypothalamus, papers by Gellhorn (824) 1953, and (823) 1952, should be studied. This author has found that the inhalation of 10 percent carbon dioxide reduces the responsiveness of specific sensory projection areas to optic and acoustic stimuli, while increasing reactivity of the hypothalamic cortical system. Gellhorn and French (826) 1953 have also found that carbon dioxide inhaled for brief periods in concentrations varying from 10–35 percent increases the frequency of topically induced cortical strychnine spikes in the normal cortex, but reduces it if the cortex is isolated from underlying structures by surgical undercutting. This result appears to be due, according to the author, to the fact that carbon dioxide exerts an excitatory effect on the hypothalamus and through increased hypothalamic-cortical discharges indirectly upon the cortex and in addition has a direct inhibitory action on the cortical gray matter of the brain. Carbon dioxide produces an inhibitory action on the "isolated" cortex since the hypothalamic-cortical influence is eliminated. Nearly complete sectioning of the inter-hemispherical transmission systems does not alter the action of carbon dioxide on cortical spikes. According to Gyarfas and Pollock (829) 1952, inhalation of 30 percent carbon dioxide and 70 percent oxygen results in an increase in the frequency and a decrease of the amplitude of cortical electrical discharges. This effect proceeds until the cortical activity becomes isoelectric, although fast bursts still appear. The sub-cortical structures studied showed less responsiveness to carbon dioxide than the cerebral cortex. There was some decrease in the amplitude and some increase in the frequency. However, the tendency to resemble cortical activity was strongest in the caudate nucleus and



less in the globus pallidus where an autonomous reaction could be discerned. The thalamus, hypothalamus and the mesencephalic structures studied exhibited an increasingly independent reaction to carbon dioxide. Electrical activity recorded from the thalamus, hypothalamus, the pallidum and mesencephalic structures was considered to be either release phenomena or idiopathic discharge. On return to room air all changes disappeared promptly regardless of the duration of carbon dioxide administration. Schaefer and Carey (862) 1953 and (863) 1954 and Schaefer, Cornish, Stuntz, Lukas, Brewer and Carey (864) 1952, have examined experimentally in human subjects the effects of exposure to various carbon dioxide concentrations upon flicker fusion frequency and alpha blocking time. Exposure of subjects to 1.5, 3.4, 5.4 and 7.5 percent carbon dioxide concentrations over periods of 20 minutes with 10 minutes allowed for dark adaptation was carried out. During this time a steady state in respiration was usually reached as indicated in respiratory minute volume and alveolar carbon dioxide. The results indicated that concentrations of five percent carbon dioxide and higher produced a significant drop in flicker fusion frequency, a decreased qualitative blocking effect, and an increased alpha blocking time. Schaefer and Barton (861) 1956, studied carbonic anhydrase activity and K and Na content in hypothalamic and cortical areas of guinea pigs exposed to 15 percent carbon dioxide in 21 percent oxygen over periods up to seven days. Carbonic anhydrase activity of the cortex increased while that of the hypothalamus decreased after seven days exposure. In the cortex the Na level was maintained while the K content declined slightly. In the hypothalamus the Na sodium content fell significantly paralleling the decrease in carbonic anhydrase activity in the reticular substance and later the hypothalamus showed bursts of three per second waves of 200–300 microvolts. These bursts were rather discreetly localized and only from time to time spread to more superficial structures. The threshold of electrical stimulation of the hypothalamus and the reticular formation decreased under 10, 15 and 30 percent carbon dioxide. Thresholds in other areas of the brain showed variable changes. According to Woodbury, Rol-

lins, Gardner, Hirschi, Hogan, Rallison, Tanner and Brodie (878) 1958, inhalation of relatively low concentrations of carbon dioxide (5–20 percent) decreases brain excitability. Inhalations of high concentrations of carbon dioxide (40 percent or higher) greatly decreases brain excitability and causes anesthesia. Abrupt removal of rats from high (anesthetic) concentrations of carbon dioxide results in spontaneous clonic seizure within 30 seconds to one minute after withdrawal. The seizures last for one to two minutes. Inhalation of 50 percent carbon dioxide decreased brain intracellular Na and K concentration and resulted in striking cellular acidosis. Thirty seconds after abrupt withdrawal of rats from 50 percent carbon dioxide, but prior to the onset of seizures, concentrations of Na in brain cells increased and the concentrations of K decreased. Sieker and Wilson (865) 1960 designed a study in human subjects to investigate the relationship of serum K levels in hypoxia and hypercapnia to changes in the EEG. It was found that acute hypoxia was associated with a significant increase in serum K, and an inconsistent change in the EEG (electroencephalographic) in this area. The K level was found only slightly lowered. The K/Na potassium-sodium ratios changed in opposite directions showing an increase in the hypothalamic area and a decrease in the cortex.

Carey, Schaefer and Delgado (818) 1955, working with monkeys have examined experimentally the effects of various carbon dioxide concentrations on electrical activity and excitability of the brain in the waking animal. In a series of monkeys multilead electrodes were permanently implanted for periods of one to three months to study the action of 5, 10, 15 and 30 percent concentrations of carbon dioxide in the air. The authors examined the motor cortex, the occipital cortex, as well as areas in the thalamus, hypothalamus and reticular substance. The pattern of the spontaneous electrical activity of each of the areas of the brain recorded on different days was rather constant throughout all the observation periods on air. After 10 minutes of exposure to 10, 15 or 30 percent carbon dioxide there was generalized slowing down and decrease in amplitude in monopolar recording of all the areas with the exception of the hypothalamus

which appeared to be less affected. With 10 and 15 percent carbon dioxide bipolar recordings of the hypothalamus and the reticular substance revealed increased occurrence of runs of five to seven cps of higher amplitude. This phenomenon was also observed when the animals were exposed to five percent. With 30 percent carbon dioxide there was an initial period of increased number of five to seven cps followed by a gradual disappearance of this activity. In some animals after 18 minutes of exposure to 15 percent carbon dioxide pattern. When subjects breathed 10 percent oxygen, 2.5 percent carbon dioxide and nitrogen mixtures, the electroencephalographic EEG pattern remained unaltered. Particularly because the arterial oxygen saturation did not fall to levels observed when carbon dioxide was not used in the mixture. With comparable levels of arterial oxygen saturation produced by breathing 7.5 percent oxygen, 2.5 percent carbon dioxide and nitrogen, the electroencephalographic EEG alterations of hypoxia were noted. The authors concluded that carbon dioxide apparently exerts a protective effect by stimulating respiration and preventing as severe hypoxia as observed when it is not used. Holmberg (831) 1954, conducted an evaluation of the effect of carbon dioxide on convulsions induced by electric shock treatment. The author studied the effects of administration of a mixture containing 6.6 percent carbon dioxide, 15.8 percent oxygen and 77.6 percent nitrogen for two minutes immediately preceding the shock. Ten percent carbon dioxide significantly prolonged the duration of the tonic phase of the convulsive seizure, but the duration of the clonic phase was not changed appreciably, nor was the peak intensity of the convulsion. During the latter part of the seizure corresponding to the clonic phase, the intensity of the convulsion was increased significantly. There was also an increase in the total amount of muscular energy developed during the seizure as a whole. The most striking effect was a very constant and highly significant increase in the frequency of the clonic jerks. The gas mixture did not affect the degree of post convulsive unrest. It was assumed by the authors that the effect of carbon dioxide administration was to increase cerebral circulation and oxygenation. The particularly pronounced effect on the

frequency of the clonic jerks may possibly indicate that subcortical structures were more strongly influenced. A direct effect on the musculature was considered to play an unimportant role. Confirmatory results were given in supplementary experiments with inhalation of a carbon dioxide-oxygen mixture, and with hyperventilation with air. Dahlberg-Parron (819) 1951, studied the effect of hypercapnia on electrically induced convulsions in rabbits. The animals were unanesthetized and uncured and were studied by recording electromyographically the activity of the gastrocnemius muscles. Hypercapnia was produced by pretreatment for 5 minutes with 12 percent carbon dioxide in oxygen. Hypercapnia was found to prolong the flexion stage that introduces the tonic phase. The subsequent extension stage was shortened as well as the total tonic phase. Conversely the succeeding clonic phase was prolonged. Also a clonic phase was produced in animals which normally had none. In a study of factors influencing the development of carbon dioxide withdrawal seizures, Carey and Schaefer (812) 1959, exposed rats to carbon dioxide concentrations of 30 and 50 percent in oxygen for various periods of time. The authors found no consistent seizure activity after withdrawal from exposure to 30 percent carbon dioxide for one hour. However, after five hours exposure to 30 percent carbon dioxide transition to air produced seizures in most animals. After exposure to 50 percent carbon dioxide for ten minutes withdrawal seizures occurred within one minute in 95 percent of the animals. Exposure to 50 percent carbon dioxide for one hour eliminated the seizure activity. The development of seizures was found to be related to: (1) a drop in blood carbon dioxide tension exceeding 100 mm. Hg and resultant decreases in brain tissue carbon dioxide content, (2) a fall in plasma calcium to approximately 2 mEq/L, and (3) significant changes in the extra and intracellular  $H_2O$  and Na content.

In studies of excised rat sciatic nerve Carpenter (814) 1961, and (815) 1963, has found that exposure to carbon dioxide (0 to 40 mm. Hg) caused a reduction in spontaneous repetitive activity as the  $pCO_2$  increased. The increased spontaneous activity in low carbon dioxide was



thought to be due to the increase in pH and consequent loss of calcium ions. The addition of carbon dioxide prevents this loss. Therman (872) 1962, has found that nerve fibers are more susceptible to temporary lack of carbon dioxide (less than five percent) than to brief periods of anoxia. Moderately increased carbon dioxide tension leads to an increase of the slow electronic component (recovery process) of the membrane potential (L fraction) and is more pronounced in small nerve fibers. Carbon dioxide increases the threshold of stimulation, decreases the speed of nerve impulse conduction, increases duration and height of the action potential, increases the ability of nerve fibers to endure prolonged stimulation and delays the onset of anoxic depolarization. Carbon dioxide also reduces the endplate potential while pure oxygen restores it. The L fraction produced by carbon dioxide requires inherent metabolic mechanisms as opposed to similar effects of an anodal current which requires a source of energy. Carbon dioxide similarly increases the L fraction in the sympathetic ganglion. Reduction of the external pH in the absence of carbon dioxide does not mimic carbon dioxide responses. The author concluded that carbon dioxide acts by participating in reactions derived from oxidative metabolism. It was believed that the central nervous system effect of carbon dioxide on the L fraction and thus on the threshold of excitability. A rapid decrease of carbon dioxide tension tends to produce "spontaneous" discharge of nerve impulses. The effects of end-tidal carbon dioxide levels have been studied by Gill (827) 1963, in single phrenic motor neurones in decerebrate cats ventilated to maintain complete oxygen saturation. As carbon dioxide levels were raised to threshold activity became irregular. Above threshold, intensity of unit discharge generally tended to increase (more rapidly at first) and often reaching a plateau. As end-tidal carbon dioxide was reduced, activity continued to show clear discharge and silent phases, becoming irregular near threshold. The threshold on decreasing the carbon dioxide level was lower than the threshold on increasing carbon dioxide.

For further studies on the effects of carbon dioxide inhalation on respiratory regulation, papers by Ngai and Wang (849) 1953, Tang

(871) 1959, Cohen (818) 1959, and Rosenstein and Borison (859) 1963, should be consulted.

Frederickson and Schenk (822) 1959, have found that asphyxia of a neuromuscular preparation in a cat (tibialis anticus-sciatic nerve preparation) causes an increase in the maximal twitch height, and augmented initial response to D-tubocurarine, and a reversal of a D-tubocurarine block. Increased carbon dioxide decreases the maximal twitch height in most experiments and this decreased twitch due to hypercarbia is transiently returned to normal by epinephrine. Hypercarbia produces an increased sensitivity of the preparation to D-tubocurarine, but has no effect on the course of a D-tubocurarine block.

Bartels and Witzleb (804) 1956, have found that the action potential in the carotid sinus nerve of cats is reduced by increasing carbon dioxide inhalation from 3.2–12.7 percent. For other studies on the effects of carbon dioxide on chemosensitivity, papers by Heymans and Neil (830) 1958, Joels and Neil (833) 1961, Loeschcke, Mitchell, Katsaros, Perkins and Konig (839) 1963, Mitchell, Loeschcke, Severinghaus, Richardson and Massion (844) 1963, and Mitchell, Massion, Carman and Severinghaus (845) 1960, should be studied.

Young, Sealy, Harris and Botwin (879) 1951, have found that hypercapnia caused by breathing 20 percent oxygen mixtures enhances the effect of vagal stimulation on the heart in adult mongrel dogs. Campbell (811) 1955, in dogs also found that hypercapnia augmented cardiac inhibition during vagal stimulation.

The effect of varying rates of concentration increase upon the analgesic potency of various concentrations of carbon dioxide in rats has been recorded by McQuarrie (840) 1961. The rats were subjected to carbon dioxide for periods of five minutes, one hour, five hours and 24 hours, during which time the concentration of carbon dioxide was increased linearly to either 5, 10 or 16 percent. The method is believed to be reliable at low carbon dioxide levels (not much over 16 percent) because anesthesia is approached. The rats had a demonstrable and statistically significant analgesic effect due to exposure to carbon dioxide in all groups except the one to a five percent carbon dioxide concentration in 24 hours. At all three concentrations

when the rate of concentration rise was both prolonged (beyond one hour in the five and ten percent groups, and to 24 hours in the 16 percent group) there was a significant attenuation of the analgesic effect of carbon dioxide. The author concluded that an animal is able to tolerate higher concentrations of carbon dioxide acutely if the rate of concentration rise is prolonged, even though the rate of concentration increase and progressive prolongation of exposure time could not be critically differentiated.

The effects of changes in carbon dioxide upon sense organs is exemplified by a study reported by Wing, Harris, Stover and Brouillette (876) 1952. Cochlear microphonics were recorded by means of an electrode placed in the round window in the ear of anesthetized cats breathing different mixtures of oxygen in nitrogen through a resuscitator. Simultaneous electrocardiographic (EKG) changes were made and changes were studied and a few observations made concerning the effects of administered carbon dioxide upon microphonics. Cochlear microphonics were reversibly reduced by carbon dioxide between 5.2 percent and 25 percent in oxygen.

According to Kollias and Bullard (835) 1963, carbon dioxide (6 percent in air) was proven to be the most effective of several procedures studied in increasing the heat tolerance of the white rat. Control rats restrained at 34°C. had a mean survival time of 154 minutes, while those breathing 6 percent carbon dioxide in air survived the entire exposure time of 240 minutes (100 percent survival). Rats breathing carbon dioxide also showed a decreased rate of body temperature increase. Survival was also enhanced by 6 percent carbon dioxide in unrestrained rats at 40°C. When the gas or air mixture was saturated with water vapor to prevent evaporative heat loss, the control rats survived a mean of 17 minutes longer than the carbon dioxide rats. This observation and direct measurement indicated to the authors that carbon dioxide protected by increasing evaporation probably from the respiratory tract rather than by the prevention of respiratory alkalosis. A similar finding has been reported by Bacharach, Snyder and Templeton (803) 1961. In dogs a 30 minute period of circulatory arrest was begun when the esophageal temperature reached 10–15°C. During cooling and rewarm-

ing, perfusion was maintained at 2 L/m<sup>2</sup>/min. One series of 15 dogs was ventilated with 100 percent oxygen, and a second series of 15 with 5 percent carbon dioxide in oxygen, both at 20 cpm with a constant flow of gas at 7 L/minute. In adults with 100 percent oxygen the brain (left cerebral hemisphere) temperature lagged 2–4° behind esophageal temperature during cooling. After the 30 minute period of arrest the brain temperature had drifted up 4–6° and the esophageal temperature up 3–5°. In the dogs with 5 percent carbon dioxide the brain temperature became 1–3° lower than the esophageal near the end of the cooling phase. After arrest the brain had drifted up 3–5°C.

In human subjects exposed to an ambient temperature of 5°C. for 75 minute periods breathing of 2.5 percent carbon dioxide was shown by Bullard and Crise (808) 1961, to inhibit shivering. After carbon dioxide inhalation shivering and metabolic rate were greatly increased. When 6 percent carbon dioxide was inhaled for 30 minutes the inhibition was overcome and shivering and metabolic activity approached high levels. Increased respiratory heat loss associated with carbon dioxide breathing may be one factor, according to the authors, causing breakthrough of the inhibition. Bullard and Crise (807) 1959, also found that all subjects breathing 10 percent oxygen and 4 out of 6 subjects breathing 12 percent oxygen showed marked augmentation of shivering activity. In these experiments return to normal air resulted in a depression of shivering.

The effects of carbon dioxide on behaviour has been reported by Goldberg, Peck, Chappell and Lipinski (828) 1962, and by Weinstein (875) 1963. The former authors gave electric shock to rats trained to press a bar for a food reward. The effect of the shock was the formation of a conditioned suppression. An experimental group of rats was then given carbon dioxide to the point of coma. On recovery these rats began to bar-press again at a significantly shorter time than the control group who had not received the carbon dioxide. It was felt that the situation was analogous to the human situation where anxiety is reduced by inhalation of carbon dioxide. Weinstein's report is that of experiments performed to determine the effectiveness



of carbon dioxide as a reinforcer in conditioning procedures. Pigeons were placed in an apparatus permitting either the investigator or the experimenter to produce stepwise changes in inspired gas concentration. In avoidance conditioning, the effect of increase in the magnitude of the change in carbon dioxide concentration upon the time elapsing between the onset of the concentration and the operant response was determined. This latent period decreased as the magnitude of the concentration change increased. It also decreased as the interval between presentations of carbon dioxide decreased. Anoxia did not elicit operant responses directed toward relieving the anoxic state. If the anoxia was not relieved by the investigator the pigeon soon expired. When inspired carbon dioxide was progressively increased the pigeons operant response rate increased adequately to maintain a constant tolerable level of inspired carbon dioxide. Ingested  $\text{NaHCO}_3$  increased the operant response rate. The relation between carbon dioxide inhalation and drug and other chemical substances has been reported by Brassfield and Sealby (805) 1961; Normann (851) 1956; Payne (852) 1960; and Woodbury and Karler (877) 1960.

Since inhalation of carbon dioxide does produce predictable effects upon the central nervous system, it may be hypothesized that it may be used as a therapeutic modality in the therapy of psychiatric conditions. The literature in this field is large and selected papers only are given in this section. The reader should consult reports by Weaver, Peterson and Anderson (874) 1951; Moriarty (846) 1952; Meduna (841) 1953; LaVerne and Herman (836) 1953; Smith (867) 1953; Silver (866) 1953; Moriarty (847) 1954; Brick (806) 1956; and Meduna (842) 1958. For a discussion of the possible physiological basis of carbon dioxide therapy and of the psychoneurosis a paper by Gellhorn (825) 1953, should be examined. Also, a paper by Fay on 20 percent carbon dioxide inhalation in muscular rigidity (821) 1953, may also be read. A special group of papers on carbon dioxide therapy for stuttering has been included. These reports are by Arthurs, Cappon, Douglass and Quarrington (802) 1954; Kent (834) 1961; and Smith (868) 1953. In connection with carbon dioxide therapy it should be pointed out that Stephens (869)

1951 has reported cellular changes in the central nervous system resulting from carbon dioxide administration in animals. Therefore caution in repeated use of carbon dioxide as a therapeutic procedure is warranted.

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### C. HEART AND CIRCULATION

Several general papers on the effects of carbon dioxide on the heart and circulation may be discussed first. Price (928) 1960, stated that in the isolated heart increased P<sub>CO<sub>2</sub></sub> reduces the contractile force and rate of contraction in various mammalian species. The ability of carbon dioxide to reduce pH is believed to be a primary factor. With few exceptions the effect of carbon dioxide is relaxation of peripheral blood vessels. It is not clear whether pH or P<sub>CO<sub>2</sub></sub> is the more important. Capillaries and veins may be most affected. Aortic and carotid body chemoreceptors are very sensitive to carbon dioxide which also affects the posterior hypothalamus, the mesencephalic reticular substance, and respiratory and vasomotor control areas further caudally. As

$P_{CO_2}$  increases, acidosis reduces body responses (roughly 50 percent at 30 percent carbon dioxide). Cardiac output is increased in normal men breathing carbon dioxide while lying supine. Vascular resistance is reduced as  $P_{CO_2}$  increases. Arterial hypertension is almost invariable during carbon dioxide inhalation, but is relatively minor. Systolic and diastolic blood pressure and heart rate are increased in healthy males. The most reliable circulatory indication of hypercarbia in anesthetized subjects is cardiac arrhythmia. Posthypercapnic hypotension occurs. Various arrhythmias, especially ventricular arrhythmias, can occur both during hypercarbia and during its correction, due probably to increased sympathetic nervous system activity. Heath and Brown (907) 1954, have reported on fall in arterial blood pressure, cardiac arrhythmias, and in some instances, ventricular fibrillation and death, following return to air breathing after inhalation of carbon dioxide for two to four hours in dogs. It has also been shown that an increase in circulating blood volume occurs during hypercapnia and persists during the period of most severe hypotension following return to air breathing. In order to determine the relative role of reduction in cardiac output and peripheral resistance in this hypotension, 30 percent carbon dioxide in oxygen was administered from an open system to pentothal anesthetized dogs. Cardiac output was determined by the direct Fick method, before, five minutes after, and two hours after the carbon dioxide breathing. The central arterial pressure was recorded continuously during the blood sampling by means of a strain gauge connected to a catheter and inserted through the carotid artery into the aorta. Within five minutes after returning the dogs to air breathing, the mean arterial pressure usually fell to approximately one-half the control level. These data indicate that a reduction in cardiac output accounts for this hypotension with no significant change in peripheral resistance at this time. When the fall in blood pressure was prevented by intravenous administration of norepinephrine, cardiac output fell to the same extent as before and the blood pressure was maintained entirely by an increase in peripheral resistance. Sechzer, Egbert, Linde, Cooper, Dripps, and Price (935) 1960, gave carbon

dioxide in oxygen ranging from 7–14 percent for periods of 10–20 minutes to human male volunteers. It was found that respiratory minute volume, arterial pressure, heart rate, and plasma concentrations of epinephrine, norepinephrine and 17-OH corticosteroids were increased in every subject during hypercarbia. Abnormal cardiac rhythms were infrequently observed. Following substitution of oxygen for the carbon dioxide-oxygen mixture, the altered measurements returned to normal over a period of roughly ten minutes. Neither marked hypotension nor cardiac arrhythmia was observed after correction of hypercarbia. A further study of carbon dioxide inhalation upon the circulation is that by Hille, Hild, Melchelke and Barth (908) 1961. In this investigation changes in muscle and skin circulation and arterial blood pressure were recorded in 12 healthy human subjects during unrestricted breathing of 7 percent carbon dioxide and during hyperventilation with approximately similar volumes of air, or 4 and 7 percent carbon dioxide-oxygen mixtures. Hyperventilation with air as well as carbon dioxide breathing resulted in a vasoconstriction of skin blood vessels. The actions of both factors were additive. Hyperventilation increased circulation in underwarm muscles, carbon dioxide breathing lowered this increased circulation. Tachycardia due to hyperventilation was lessened by carbon dioxide. The blood pressure fell during hyperventilation with air while during carbon dioxide breathing it was regularly increased. The authors concluded that circulatory changes brought about by carbon dioxide breathing and those effected by hyperventilation as a result of carbon dioxide breathing are independent of one another. Circulatory reactions to hyperventilation with air are not considered a result of hypocapnia. The authors believe they are probably caused by stimulation of the sympathetic nervous system and release of adrenaline.

Breathing carbon dioxide mixtures tends to decrease cardiac contractile force. This has been demonstrated in acute experiments by Boniface and Brown (884) 1953, using a modified Cushny myocardiograph to measure the effect of carbon dioxide mixtures on the contractile force of a representative segment of the right ventricle.



With reduction in contractile force there was also a decrease in the amplitude of systolic excursion. Pronounced cardiac dilatation also occurred. The extent and rapidity of these changes were roughly proportional to the concentration of carbon dioxide in the respired gases. Carbon dioxide differed from the common and typical cardiac depressants in that the heart sometimes regained its original contractile force during continuous administration of carbon dioxide and again when the gas was withdrawn a characteristic and marked 'rebound' effect sometimes appeared. In isolated rabbit auricles, Vaughan-Williams (942) 1955, found that carbon dioxide had a specific effect upon conduction velocity. The higher the carbon dioxide concentration, the faster the velocity of conduction. At a constant carbon dioxide concentration the conduction velocity was to some extent increased by alkali and decreased by acids. Monroe, French and Whittenberger (922) 1960, found that moderate elevations of  $P_{CO_2}$  (61–75 mm. Hg) did not consistently depress myocardial contractility in mongrel dogs as determined by standard ventricular function curves. With an altered preparation in which the heart rate and left atrial pressure were held constant, a  $P_{CO_2}$  of 60–75 mm. Hg was accompanied by an average reduction in stroke work to 73.6 percent of control value, while hypocapnia with an alveolar  $P_{CO_2}$  of 6–13 mm. Hg was unaccompanied by any consistent reduction in stroke work.

The tolerance of the dog heart to carbon dioxide has been studied by Brown and Miller (886) 1952 and (887) 1952. When the carbon dioxide concentration in the inhaled air was gradually increased over a period of 60–90 minutes, most dogs reached levels above 90 percent before the blood pressure fell to zero and cardiac arrest followed. The average pH of the last arterial blood sample drawn was 6.41. A gradual slowing of heart rate and a slight increase in P–R interval regularly accompanied the increasing carbon dioxide tension. Respiratory arrest usually appeared when the carbon dioxide concentration reached 60–65 percent and artificial respiration was required above this concentration. Blood pressure usually started to fall when the carbon dioxide concentration reached 50–70 percent, and cardiac arrest followed a

severe fall in blood pressure. For other studies on cardiac tolerance to carbon dioxide papers by Bücherl and Kloos (888) 1960, and Clowes, Hopkins, and Simeone (890) 1955, may be consulted.

Sealy, Young and Harris (943) 1954, have suggested hypercapnia is a factor in the pathogenesis of cardiac arrest. The critical period for the heart is the posthypercapnic period. Posthypercapnic ventricular fibrillation can be prevented by intravenous injection of 20 percent glucose and 3 percent sodium chloride when warning electrocardiographic changes develop. Brown (885) 1955, suggests that the elevated plasma potassium is not sufficient to produce the severe cardiac effects following hypercapnia, but that a rapid decrease in arterial  $P_{CO_2}$  and hydrogen ion concentration in the presence of the sub-lethal potassium concentration may produce cardiac arrest or ventricular fibrillation. Young, Sealy, and Harris (945) 1954, studied the effects of acute prolonged hypercapnia on electrolyte metabolism and on electrocardiograms in dogs and rats. When breathing 30–45 percent carbon dioxide these animals showed a progressive rise in plasma potassium concentration. In the immediate posthypercapnic period there was an additional sharp increase in the plasma potassium level. At the same time serious electrocardiographic disturbances frequently appeared and terminated in ventricular fibrillation or cardiac arrest. The authors advance the hypothesis that the rise in plasma potassium concentration is the primary cause of the electrocardiographic abnormalities, although secondary and less specific factors may play roles. Hypertonic glucose and saline solution have been found effective in reversing the electrocardiographic changes if given sufficiently early. These results have implications in human cardiac arrest occurring during surgery. Cardiac arrhythmias and ventricular fibrillation resulting from rapid reversal of hypercarbia have been studied by Andrews, Adrian and Gordon (880) 1957, and Gordon, Andrews, Adrian and Beattie (902) 1957. Cardiac arrhythmias and ventricular fibrillation have been reported following rapid reversal of hypercarbia in animals, and this process has been implicated also in human cases of ventricular fibrillation occurring during or immediately after surgery. In the study by An-

draws, Adrian and Gordon, nembutalized dogs rebreathed into a bag for periods of 90 minutes. The dogs were then rapidly hyperventilated with room air. EKGs and carotid artery blood pressure were recorded continuously; serial arterial plasma pH, carbon dioxide content, and potassium were measured as often as every minute during periods of rapid change. The plasma potassium reached peaks of 50 percent above the control levels within ten minutes after the onset of rebreathing. It then fell gradually to values slightly above the control and remained there until the carbon dioxide was blown off, at which time it reached a second peak more rapidly and higher than the first. The height of the second peak correlated with the speed of carbon dioxide elimination. The EKG was essentially unchanged until the carbon dioxide was removed when ominous arrhythmias developed in 50 percent of the dogs and ventricular fibrillation in 20 percent. The severe arrhythmias occurred in dogs having the most rapid removal of carbon dioxide. The  $P_{CO_2}$  reached levels of over 300 mm. Hg, but could be brought to subnormal levels with two to three minutes by hyperventilation. This gradual accumulation of endogenous carbon dioxide and its subsequent rapid removal results in changes similar to those described after breathing 30–40 percent  $CO_2$  for two to four hours, or with sudden reversal of hypercarbia during and immediately following surgery. In the paper by Gordon, Andrews, Adrian and Beattie, the anesthetized dogs rebreathed continuously from a large rubber bag for 90 minutes, into which oxygen was replaced as needed, and then were hyperventilated with air for one minute. A second series of dogs was given 0.05 mg. of epinephrine per kilogram body weight intravenously at the beginning of a rapid reversal of hypercarbia. In the first series during carbon dioxide retention the arterial  $P_{CO_2}$  rose gradually from 38 to 247 mm. Hg at 90 minutes; the pH fell from 7.42 to 6.82, and the plasma potassium K had a transient rise (within the first two minutes) and gradually returned to normal. With hyperventilation the  $P_{CO_2}$  dropped to a subnormal level of 25 mm. Hg while the pH made an alkalotic swing to 7.5 within two to three minutes and persisted, and the potassium K rose from 4.6 to 5.7 mEq/l at four

minutes, returning to normal within five minutes. Initially during rebreathing all dogs showed sinus tachycardia, tachypnea, and rising blood pressure; but after one hour they exhibited progressive slowing of pulse and respiration and decrease in blood pressure. During hyperventilation, cardiac arrhythmias, A–V dissociation, ventricular extrasystoles and tachycardia occurred in all dogs. There was a brief pulse acceleration and systolic blood pressure rise followed in most cases by a relative bradycardia and hypotension. The results of the second series were the same except that the plasma potassium K almost doubled within two minutes after the onset of hyperventilation and EKG changes were more severe. Posthypercapnic bradycardia and hypotension were prevented.

Of the physiological factors important in the regulation of cardiac output, blood  $P_{CO_2}$  has been investigated relatively little. Richardson, Wasserman, Dingleline and Patterson (930) 1959, reported striking changes in hemodynamics associated with hypercapnia induced by breathing 7 percent carbon dioxide for seven minutes in 16 experiments in 10 normal human volunteers. In additional experiments subjects performed maximal voluntary hyperventilation with a variable inspired carbon dioxide concentration adjusted to maintain constancy of end-tidal  $P_{CO_2}$ . During voluntary hyperventilation with alveolar  $P_{CO_2}$  maintained at control levels, the average respiratory minute volume of the group increased from 13 to 33 liters, and the average cardiac index remained constant at 3.6 L/min/m<sup>2</sup>. During breathing of 7 percent carbon dioxide there was an increase in respiratory minute volume from 9 to 45 liters, in  $P_{CO_2}$  from 42 to 58 mm. Hg, and in cardiac index from 2.9 to 4.2 L/min/m<sup>2</sup> ( $p < 0.001$ ). Mean arterial pressure rose from 89 to 105 mm. Hg ( $p = 0.001$ ) during 7 percent carbon dioxide breathing but rose only 3.5 mm. Hg ( $p = 0.1$ ) during vigorous breathing without change in  $P_{CO_2}$ . The reported results demonstrated to the authors that the large alterations in circulatory dynamics associated with induced hypercapnia are the results of changes in blood  $P_{CO_2}$  and not of the vigorous respiratory movements. The thorax apparently does not act as a blood pump during hyperventilation. In dogs, Li, Kao, McCoy and Harmel



(916) 1961, found no significant change in cardiac output in hypercapnia.

Feinberg, Gerola and Katz (898) 1958, and (899) 1960, studied the effects of changes in blood carbon dioxide level on coronary flow and myocardial oxygen consumption. The effect of hypo- and hypercapnia induced by changing the respiratory gas mixture on coronary flow and myocardial oxygen consumption was observed at constant cardiac output and over a broad range of pressure loads in open-chested anesthetized dogs. The correlation of cardiac effort (as indexed by the product of heart rate and mean aortic blood pressure) with myocardial oxygen consumption was not altered by increasing or decreasing the arterial carbon dioxide content. Coronary blood flow was observed to be increased relative to the cardiac effort during hypercapnia but not during hypocapnia. The coronary arteriovenous oxygen differences and the percentage of oxygen extracted decreased during hypercapnia *'pari passu'* with the increase in venous oxygen content.

Several studies of the effects of carbon dioxide on peripheral circulation have been carried out. McArdle, Roddie, Shepherd and Whelan (920) 1957, examined the effect of inhalation of 30 percent carbon dioxide for one to two minutes on the cardiovascular system in men undergoing carbon dioxide treatment for stammering. There was increased activity of respiratory muscles due to increase in depth and, to a lesser extent, rate of respiration. Consciousness was dulled and sweating profuse. Blood flow through the normal forearm and calf showed a transient increase followed by a decided fall (on occasion almost ceasing). Peak flow after carbon dioxide was two to five times greater than the control. Since there was an associated increase in arterial blood pressure (i.e. 125/75 to 205/110) during carbon dioxide inhalation, the decrease in flow was due to intense vasoconstriction, probably deep to the skin because oxygen saturation in superficial venous blood did not fall. There was a slight decrease in blood flow through the forearm despite the increased blood pressure, when in one case the nerves of the forearm were blocked with local anesthesia, suggesting that nervous vasoconstriction cannot completely account for the marked decrease in muscle flow.

Changes in hand blood flow were equivocal. McArdle and Roddie (919) 1958, administered 30 percent carbon dioxide for one to two minutes to young women following minor gynaecological surgery and after general anesthesia. This procedure led to hyperpnea, eliminating volatile anesthetics and therefore causing rapid return to consciousness. The conscious patients exhibited 120/75 to 210/100 mm. Hg rise in arterial blood pressure accompanied by slowing of the heart. Forearm blood flow after transient increase was greatly reduced to almost zero. If the forearm was nerve-blocked, a similar fall did not occur, implicating vasomotor nerves in vasoconstriction. In the normal forearm, on cessation of carbon dioxide inhalation, there was a transient vasodilatation. With anesthesia the responses were modified; arterial blood pressure was only slightly increased, heart rate increased slightly with little or no change in blood flow and no transient vasodilatation initially. Transient vasodilatation did occur on cessation of carbon dioxide inhalation, however. The respiratory response was depressed, but arterial pH was comparable to that in a conscious subject. Evidence indicates to the authors that alterations in response during anesthesia were due to general depression of reflex activity. Local injection of carbon dioxide into the skin, or immersion of the hand in water saturated with carbon dioxide have been found by Diji and Greenfield (894) 1958, and (895) 1960, and Diji (893) 1959, to exert local vasodilator action. For further studies on peripheral vasodilatation following carbon dioxide inhalation in man, papers by Black and Roddie (882) 1958; and Blair, Glover, McArdle and Roddie (883) 1960, may be consulted.

Carbon dioxide inhalation has been shown to increase cerebral blood flow. This cerebral blood flow response to carbon dioxide is greatly reduced in cerebral vascular disease. Patterson, Heyman, Battey and Ferguson (925) 1955, have reported that the vasodilator response of normal cerebral vessels to rapid increase in arterial  $P_{CO_2}$  appears to be a threshold type of phenomenon. In a group of 28 subjects a mean increase in arterial  $P_{CO_2}$  of less than 4.5 mm. Hg was without vascular effect, whereas increases greater than this value produced progressive vasodilatation. In-

halation of 3.5 percent carbon dioxide produced a ten percent mean increase in cerebral blood flow. For other studies of the effects of carbon dioxide inhalation on cerebral circulation papers by Hafkenschiel and Friedland (904) 1952; Novack, Shenkin, Bortin, Goluboff and Soffee (924) 1953; Schieve and Wilson (932) 1953; Wilson, Odom and Schieve (944) 1953; Hansen, Sultzter, Freygang and Sokoloff (906) 1953; Sokoloff (937) 1960; Lambertsen, Semple, Smyth and Gelfand (915) 1961; and Rapela, Machowicz and Freeman (929) 1963, should be consulted.

According to Stroud and Rahn (940) 1953, and Fishman, Fritts and Cournand (900) 1960, inhalation of carbon dioxide did not produce pulmonary vasoconstriction. On the other hand Stroud (939) 1962, stated that high carbon dioxide, and more strongly and definitely, low oxygen caused resistance to blood flow through the lungs due to vasoconstriction. The vasomotor response to changes in gas tensions is stated to be neurogenic with both thoracic sympathetic outflow and the vagus nerves implicated.

Epstein, Wheeler, Frumin, Habif, Papper, and Bradley (897) 1961, found that estimated hepatic flow, splanchnic blood volume, calculated splanchnic vascular resistance and mean arterial pressure, did not change significantly or consistently during light general anesthesia with thiopental and nitrous oxide, maintained by mechanically controller artificial respiration following neuromuscular blockade with succinylcholine. Hypercapnia ( $\text{PaCO}_2$  56 mm. Hg on the average) under these circumstances resulted in statistically significant increment in mean calculated splanchnic vascular resistance. The estimated hepatic blood flow was decreased, remained unchanged, or rose, depending upon the behavior of arterial blood pressure. The average value for circulatory splanchnic volume also decreased significantly. These changes were ascribed by the authors to a combination of arteriolar and venous constriction. Sulphobromophthalin clearance and extraction by the liver, although unaffected by anesthesia, decreased significantly during hypercapnia.

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#### D. BLOOD

The disturbances in plasma volume, thiocyanate space and cellular components of the blood during diffusion respiration and during inhala-

tion of oxygen or mixtures of 20 or 40 percent carbon dioxide in oxygen have been investigated in the dog by Arends, Rayburn, Draper and Whitehead (947) 1952. Severe hypercarbia, whether brought by diffusion respiration or by inhalation of carbon dioxide in oxygen, results in a striking increase in plasma volume, an irregular increase in thiocyanate space and substantial increases in the red cell count, red cell volume and oxygen capacity of venous blood. There is no change in either the white or differential count. In a general review paper on carbon dioxide and respiration in acid-base homeostasis, Lambertsen (958) 1960, discusses the respiratory response to concentrations of carbon dioxide from 0 to 6 percent. The response of respiratory neurons to deviations in local environment plays the dominant role in the total process responsible for acid-base and oxygen homeostasis. In responding to local changes the respiratory neurons cause alterations in the acid-base composition of arterial blood and other fluids which modify the local environment of many other cells. Only the small fraction of these cells showing intrinsic reactivity to acid-base change are capable of responding and therefore acute active homeostatic regulation of the internal environment is restricted to these reactive cells. These cells, including central respiratory neurons, vascular smooth muscle cells and chemoreceptor glomus cells, exist in their most stable states at entirely different acid-base levels and provide independent sensing components in the fluctuating dynamic interaction of factors concerned with acute adjustment of the acid-base composition by the total respiratory control mechanism.

Hypoxemia in the presence of severe hypercapnia is commonly assumed to be due to the Bohr effect. In order to determine the influence of this effect, MacArthur and Brown (961) 1958, have determined oxygen dissociation curves on dog's blood at carbon dioxide tensions of approximately 40, 200, 350 and 430 mm. Hg. Blood pH was determined on some of the samples after equilibration with the proper gas mixture. The curves indicate that hemoglobin is approximately 90 percent saturated at an oxygen tension of 175 mm. Hg and a carbon dioxide tension of 430 mm. Hg (pH 6.55). With a carbon dioxide tension of 340 mm. Hg (pH 6.65) blood was



saturated 95 percent at an oxygen tension of 150 mm. Hg. It seems unlikely that displacement of the oxygen hemoglobin dissociation curve due to high carbon dioxide tension is responsible for an appreciable degree of oxygen unsaturation as long as (at sea level) 25–30 percent of the alveolar gas is oxygen. The Bohr effect (Margaria (962) 1962) refers to the increased acidic properties of hemoglobin as a consequence of oxygenation. The effect of varying carbon dioxide tensions on the oxyhemoglobin dissociation curves under hypothermic conditions have been studied by Callaghan, Lister, Patton and Swan (952) 1961. Experiments were designed to investigate the effects of different carbon dioxide tensions on the oxygen dissociation curve of blood at various temperature levels using a rotating disc oxygenator as a tonometer. Variations in hematocrit were shown to be inept in construction of curves obtained. Rising carbon dioxide tension moves the dissociation curve to the right, and flattens it in shape at all temperatures studied; and raising carbon dioxide tension opposes the effect of simultaneous fall in temperature. In a study of tissue carbon dioxide dissociation curves Schaefer and Carey (971) 1959, exposed guinea pigs and rats to carbon dioxide concentrations of 15 percent, carbon dioxide in air, and 30 and 50 percent carbon dioxide in oxygen, for various time intervals. Carbon dioxide content, pH, and electrolytes of blood and tissues were determined and time curves established. Carbon dioxide dissociation curves of individual organs showed significant differences; slopes ranked in the order of blood, heart, kidney, liver, hypothalamus, cortex, and muscle, and are influenced by: individual differences in electrolyte exchange, blood content, and carbonic anhydrase activity. The time required to reach a steady state in tissue carbon dioxide concentration varied with the slope of the carbon dioxide dissociation curve being longest for blood and shortest for muscle. Periods between onset of exposure to carbon dioxide and the attainment of a steady state in carbon dioxide content of all organs increased with decreasing carbon dioxide concentrations and appeared to be related to a reduced speed of the processes involved in the compensation of acidosis. The effect of carbon dioxide inhalation is to lower

the pH, as has been shown by Platts and Greaves (968) 1957. In these authors' studies acute respiratory acidosis was induced in four normal persons by inhalation of seven percent carbon dioxide in air. Acute respiratory acidosis produced a greater reduction in the pH of both plasma and red cells than does chronic respiratory acidosis. The pH in the red cells in chronic respiratory acidosis is almost normal. In acute respiratory acidosis,  $\text{Cl}^-$  passes from the plasma to the red cells so that the concentration of the  $\text{Cl}^-$  in the cells rises. In chronic respiratory acidosis the concentration of  $\text{Cl}^-$  in the red cells is normal although the plasma  $\text{Cl}^-$  is very low. Chloride is lost from the blood. The patients studied in this experiment were several emphysematous and showed low concentrations of hemoglobin in their red cells. This may increase the efficiency with which the red cell contents are buffered in this condition. The anoxia of patients with chronic respiratory acidosis does not account for the changes in the composition of their blood. In a study of the influence of Diamox on posthypercapnic sequelae, Brown and Hayden (951) 1956, found that the rate of rise of arterial blood pH paralleled the rate of rise of blood pH after hypercapnia was determined during the first 10 minutes after switching from 30 percent carbon dioxide to oxygen, with and without administration of Diamox. With Diamox (50 mg/kg), the rate of rise of pH was significantly slower than it was in the control run. The nature of the carbon dioxide titration curve in the normal dog has been studied by Cohen, Brackett and Schwartz (953) 1964. In these studies unanesthetized dogs were used in a chamber with different carbon dioxide levels. Each dog was exposed abruptly to the carbon dioxide and then held there for six hours (8, 12 and 18 percent carbon dioxide). Blood samples were drawn at one, two, four and six hours. No dog was exposed twice. Their data demonstrated that increasing degrees of hypercapnia induced a curvilinear rise in extracellular  $\text{HCO}_3^-$  and the  $\text{HCO}_3^-$  fell as the  $\text{P}_{\text{CO}_2}$  rose. On the other hand, changes in  $\text{P}_{\text{CO}_2}$  induced linear changes in  $\text{H}^+$  concentration over the entire range of carbon dioxide tensions studied. These studies suggest that whole body titration with carbon dioxide may provide a useful means

for detecting experimentally induced changes in whole body buffer characteristics.

Balance studies have been conducted in dogs by Schwartz, Hays, Polak and Haynie (972) 1961, during recovery from chronic respiratory acidosis induced by high carbon dioxide atmospheres. Four animals received high salt diets and four others low salt diets during periods of exposure to carbon dioxide, and each group was maintained on the same diet throughout the recovery period. At the end of the carbon dioxide administration plasma  $\text{HCO}_3^-$  ranged from 35–39 mEq/L, and plasma  $\text{Cl}^-$  rose simultaneously was depressed. After being returned to room air the high-salt dogs showed prompt reduction in plasma  $\text{HCO}_3^-$  to a normal range (21–24 mEq/L), and plasma  $\text{Cl}^-$  rose simultaneously to a normal level. In contrast, low-salt dogs had significantly smaller reductions in plasma  $\text{HCO}_3^-$  to values of approximately 27–30 mEq/L, and became mildly alkalotic. Plasma  $\text{Cl}^-$  showed little or no change. The fall in plasma  $\text{HCO}_3^-$  in both groups usually took place without loss of  $\text{HCO}_3^-$  into the urine. During the subsequent six days, low-salt dogs stabilized plasma  $\text{HCO}_3^-$  levels in a range consistently above normal. Plasma  $\text{Cl}^-$  in these animals remained grossly subnormal. Persistent elevation of plasma  $\text{HCO}_3^-$  in low-salt animals produced an elevated rate of  $\text{H}^+$  secretion which persisted, despite normal plasma  $\text{P}_{\text{CO}_2}$ . Potassium deficiency did not appear to be factor in the difference observed between the low and high-salt groups. When salt was added to the diet of low-salt dogs, plasma  $\text{HCO}_3^-$  fell to normal and there was a reciprocal rise of plasma  $\text{Cl}^-$ . Reduction in  $\text{HCO}_3^-$  was achieved without urinary  $\text{HCO}_3^-$  loss, but was associated with marked suppression of acid excretion. Two additional studies of animals given diets low in  $\text{Na}^+$ , but containing moderate amounts of  $\text{Cl}^-$ , demonstrated that the acid-base distribution and hypochloremia could be corrected solely by provision of  $\text{Cl}^-$ .

Plasma  $\text{K}^+$  is increased by inhalation of carbon dioxide. In a study of mongrel dogs anesthetized with Pentothal, Brown (950) 1955, administered 30 percent carbon dioxide in oxygen for two hours, followed by 40 percent carbon dioxide in oxygen for two hours, and then returned to air. Potassium determinations were carried out on a

protein-free filtrate of plasma with a flame photometer. The mean plasma  $\text{K}^+$  increased during the carbon dioxide breathing as follows: controls 3.9; 15 minutes, 4.1; 30 minutes, 4.2; 1 hour, 4.8; 2 hours, 5.6; 3 hours, 5.8; 4 hours, 6.1. Following return to air the mean values for 12 dogs were 6.7 after 5 minutes, 5.6 after 30 minutes and 4.7 after one hour. All values are expressed in mEq/L. The gradual rise over the first two hours of high carbon dioxide breathing with the level remaining high over the next two hours is in contrast to the rapid rise during the first 15 minutes, with subsequent return toward normal which has been reported previously in cats. The additional rise within the first five minutes after return to air breathing was a regular finding in the dog. This is qualitatively similar to changes reported in cats breathing comparable mixtures.

The effects of carbon dioxide on relative red cell volume has been reported by Jackson and Nutt (955) 1954. The effect of a range of carbon dioxide tensions from 5–700 mm. Hg in room air on relative red cell volume, as measured by the Meyerstein hematocrit, was studied in the ox, sheep, rabbits and in human subjects. Red cells of all species investigated swelled with increasing carbon dioxide tensions up to seven percent of the cell volume in room air, in ox and sheep, up to 13 percent and up to 9 percent in human blood. Over the limits of the physiological range, that is to say from 40–60 ml. of carbon dioxide per 100 ml. of blood, there was no significant change in relative red cell volume. A second series of experiments was performed exposing sheep, rabbit and human bloods to approximately 100 percent carbon dioxide, oxygen and nitrogen. The high carbon dioxide mixture alone caused a significant change in relative cell volume. Therefore the red cell swelling observed throughout this work may be assumed to be due to carbon dioxide itself and not to changes in the state of oxygenation of the particular blood sample. A third series of experiments, in which the effect of carbon dioxide saturation was studied for times from 5–60 minutes, showed no significant increase in the degree of swelling of the cells up to 40 minutes equilibration, and only a slight increase thereafter. In a study of blood sugar and absolute eosinophile response in the rat exposed to 30 percent carbon dioxide in



air and in oxygen, King, Mego, Williams and Schaefer (957) 1953, exposed highly inbred animals of the Wistar-Hisaw strain ( $70 \pm 10$  days of age) to 30 percent carbon dioxide in air and 30 percent in oxygen in a plastic chamber over a period of one hour and allowed recovery in air in the same chamber for three hours. Blood samples were taken from the tail vein prior to exposure, during exposure, at intervals of 10, 30 and 60 minutes, and 3 hours after exposure. Determinations were made of total blood sugar, absolute eosinophile counts, differential counts, hemoglobin, carbon dioxide and oxygen content. The results indicated that during exposure to carbon dioxide, both in air and in oxygen, there was a marked rise in blood sugar but no significant change in the eosinophile count. The white blood count increased and the hemoglobin decreased slightly. There was a significant drop in eosinophiles and lymphocytes during the recovery period while the blood sugar returned to normal. These responses were essentially the same in exposure to carbon dioxide in air and in oxygen, although the oxygen content of the blood of the animals exposed to carbon dioxide in air dropped to hypoxic levels, while in those animals that were exposed to carbon dioxide in oxygen, the oxygen content of the blood remained practically normal. These results indicated that under high carbon dioxide glycogenic effects were produced independently of any changes in absolute eosinophiles.

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### E. CEREBROSPINAL FLUID

According to Leusen (982) 1963, in acute acidosis produced in dogs by breathing carbon dioxide the cerebral spinal fluid changes rapidly follow those of the blood, while changes produced by ammonium chloride, lactic acid or hydrochloric acid, were not followed by the same CSF changes. Small, Weitzner and Nahas (984) 1958, have reported changes in the CSF pressures measured in the cisterna magna during apneic oxygenation in dogs. The CSF pressure rose an average of 88 percent within the first two minutes of apnea, from an average control value of 12.3 cm.  $H_2O$  of water. The average peak increase (375 percent) occurred at an average time of 8.5 minutes, although the total period of apneic oxygenation averaged 17.6 minutes. Because the increased carbon dioxide appeared to be responsible for this rise, five of the seven dogs were ventilated with 5-25 percent carbon dioxide in oxygen after arterial, venous, and CSF pressures had returned to control values. This resulted in consistent similar rises in CSF pressure, again without parallel increases in arterial pressure. Venous pressure changes tended to parallel CSF pressure changes, but the degree of response was usually much less than that of the cerebrospinal fluid, and in some cases was absent. The initial rises in CSF pressure was interpreted as being due to cerebral vasodilatation. The later changes may be related to CSF production and absorption, and arterial and venous pressure. These studies have been reported in more detail

by Small, Weitzner and Nahas (985) 1960. The effect of carbon dioxide inhalation on the blood-brain barrier has been examined by Clemmedson, Hartelius and Holmberg (975) 1956, in experiments performed on rabbits to various concentrations (10, 15, 20 and 30 percent) of carbon dioxide in oxygen in a gas chamber. Exposure times varied from 2-60 minutes. Ten minutes before exposure a trypan blue solution was injected intravenously. Ten minutes after the exposure the animals were killed and their vessels washed out with normal saline followed by a 20 percent formalin solution for fixation. On serial frozen sections the whole brains were examined for blue stainings and hemorrhages. Thirty percent carbon dioxide for two minutes scarcely caused any obvious changes; but after three minutes of exposure more consistent effects were seen. After 4, 5 and 10 minutes exposure the changes were more pronounced, consisting of well-defined multiple stainings as well as hemorrhages. After 15 minutes or more the changes often were maximal. Some of these brains were almost totally blue, and there were rich hemorrhages in the brain substance and the meninges. In animals exposed to lower concentrations of carbon dioxide the changes were proportionally less pronounced and occurred only after somewhat longer exposure. However, with as little as 10 percent carbon dioxide and 15 minutes exposure clear changes were seen. The damage to the walls of the blood vessels obviously was reversible within a short time, which was shown by the fact that when trypan blue was injected a few minutes after the gas exposure, the stainings were only slight and the hemorrhages were unstained. The authors raised the question whether or not the cause of the barrier damage was a vigorous dilatation of the thin-walled vessels or possibly a direct toxic effect on the endothelial membranes. The results indicate to the authors that hypercapnia is a factor that should not be disregarded as a cause of cerebral damage, for example, in asphyxia, where the component of anoxia sometimes seems to have been overemphasized. These studies are more fully described by Clemmedson, Hartelius and Holmberg (976) in 1958, in which not only rabbits were studied, but also guinea pigs and cats. Guinea pigs showed similar changes to those in rabbits.



The capillaries in the cats seemed to be more resistant, but changes of the same kind only less pronounced were nevertheless observed. It is possible, according to the authors, that carbon dioxide is a physiologic regulator of permeability of the brain capillaries, as well as being a means of enhancing the penetration of pharmacological agents to the brain. Lending, Slobody and Mestern (981) 1961, have also examined the effect of hypercapnia on the blood cerebral spinal fluid barrier. The effect was evaluated in puppies and adult dogs by measuring the rate of passage of radioactive iodinated human serum albumin from plasma into the cerebrospinal fluid and by determining the plasma and cerebrospinal fluid glutamic oxalacetic transaminase and lactic acid dehydrogenase activities. In the puppies there was an increase in the blood brain transmission, but in adult dogs hypercapnia did not result in comparable findings.

The dynamics of change in respiration and arterial blood and cerebrospinal fluid acid base parameters during administration and withdrawal of carbon dioxide have been studied by Lambertsen, Wollman and Gelfand (980) 1961. Following both administration and withdrawal of 7 percent carbon dioxide in anesthetized dogs, respiratory minute volume changed more slowly than arterial pH and  $P_{CO_2}$  but more rapidly than cerebrospinal fluid pH and  $P_{CO_2}$ . On administration of 7 percent carbon dioxide blood pH fell 0.131, while the cerebrospinal pH fell 0.117, and the respiratory minute volume rose 15.6 L/min. in 30 minutes. The changes were exponential, with approximate half times of less than one minute for arterial pH, two minutes for respiratory minute volume, and five and a half minutes for cerebrospinal fluid pH. On withdrawal of carbon dioxide, changes were similar in magnitude but more rapid. Arterial pH rose 0.143, cerebrospinal fluid pH rose 0.135 and respiratory minute volume fell 13.8 L/min. in 30 minutes. Approximately half times were less than one half minute for arterial pH, one minute for respiratory minute volume and five minutes for cerebrospinal fluid pH. An overshoot of 0.026 in arterial pH was maximal at three minutes and compensated at five minutes. The differences between rates of change between arterial pH,

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## F. RESPIRATION

Acute studies generally indicate an increase in respiratory activity from breathing high carbon dioxide mixtures. A level of  $P_{CO_2}$  is reached at which ventilatory depression occurs. For general

studies of the effects of carbon dioxide excess papers by Aström (991) 1952, and Asmussen (989) 1963, should be consulted.

Froeb (1023) 1960, has conducted a study to compare the ventilatory response of SCUBA divers and nondivers to carbon dioxide inhalation under ambient conditions, at rest and during light exercise. Although there was some tendency for the SCUBA divers to have a slightly lower ventilatory response at rest, there was not a clear-cut difference. It appears that the response to carbon dioxide had no relation to the time spent in diving. Tank instructors, who hold their breath during dives, demonstrated an increased tolerance of carbon dioxide (Bond and Schaefer (996) 1962). There are individual differences in sensitivity to carbon dioxide. Schaefer (1065) 1954, has examined these group differences in carbon dioxide response of human subjects. The carbon dioxide response was studied in 70 persons, using concentrations of 1.5, 3.3, 5.4 and 7.5 percent carbon dioxide. These studies permitted a differentiation of a low and a high ventilation group on the basis of a quantitative difference in ventilatory response to 5.4 and 7.5 percent carbon dioxide. Subjects of these two groups also differed in their normal respiratory pattern in air. The low ventilation group showed larger tidal volume, smaller respiratory rate and higher alveolar carbon dioxide. The high ventilation group exhibited smaller tidal volume, higher respiratory rate and lower alveolar carbon dioxide. The low ventilation group also showed during exposure to 7 percent carbon dioxide a lower pulse rate increase, a lower blood sugar increase and a lesser eosinopenia. Schaefer (1066) 1958, also reported that subjects with a high sensitivity to carbon dioxide were found to have a high sensitivity to low oxygen, and vice versa. The differences in the ventilatory response to carbon dioxide appears to be correlated with differences in the adrenal sympathetic response to carbon dioxide. The respiratory response to carbon dioxide is discussed by Schaefer as a possible physiological selection test for underwater swimmers. Lanphier (1040) 1956, has noted that certain divers tend to develop high carbon dioxide levels during work while breathing nitrogen-oxygen mixtures at depth. This tendency is believed to be related to respiratory sensitivity

to carbon dioxide, and the latter might thus form the basis of practical personnel selection tests.

Chapters by Lambertsen (1035) 154, and (1036) 1963, should be consulted for authoritative discussions on the factors in the stimulation of respiration by carbon dioxide. The respiratory minute volume reaches a peak in man between 16 and 20 percent carbon dioxide. Lambertsen (1036) 1963, concludes that there are not two qualitative types of respiratory stimulation (pH and carbon dioxide), but that there is only *one* carbon dioxide induced stimulus, namely a change in hydrogen ion concentration which is altered at different rates at two different sites and is responsible for the carbon dioxide respiratory response at rest. A change in the hydrogen ion concentration of arterial blood, while it certainly alters the environment of the peripheral chemoreceptors, can conceivably also affect the level of central acid-base stimulus. Also, Loeschcke, Koepchen and Gertz (1048) 1958, have concluded that hydrogen ions and not carbon dioxide contribute to driving lung ventilation. In these authors' studies the fourth ventricle and adjacent areas of the brain in cats were perfused with isotonic bicarbonate buffers equilibrated with carbon dioxide. Carbon dioxide tension and pH of the perfusion fluids were varied separately. Respiratory volumes were recorded. Loeschcke and Mitchell (1049) 1963, stated that when the  $P_{CO_2}$  is increased in the cerebrospinal fluid perfusate the ventilation is increased, but when the pH is kept constant the ventilation is diminished. Apparently in the opinion of the authors the stimulation is due to an acid shift inside the cell. A review of the effects of arterial carbon dioxide and hydrogen ion concentrations, as independent additive respiratory stimuli, has been provided by Perkins (1056) 1963.

In studies by Dejours, Labrousse, Raynoud and Flandrois (1015) 1958, men breathed gas mixtures with 6.9 percent carbon dioxide to produce a hypercapnia. The response to the carbon dioxide was more intense when the subjects had been made hypocapnic prior to breathing carbon dioxide. Schaefer, Cornish, Lukas and Carey (1069) 1952, carried out studies in which 38 male subjects, after resting for 30 minutes,



breathed gas mixtures containing 3.3, 5.4 and 7.5 percent carbon dioxide for 15 minutes, followed by 15 minutes breathing air. Respiratory and circulatory responses were used to compile a carbon dioxide toxicity chart. The increase in respiratory minute volume during exposure to 3 and 5 percent carbon dioxide was produced by increased tidal volume only. With 7 percent carbon dioxide the respiratory rate was unchanged, and at 5 percent there was a small (4 percent) increase, and at 7 percent there was a 24 percent increase. Alveolar carbon dioxide and oxygen tensions were continuously measured and in most subjects plateaued within 10 minutes of 7.5 percent carbon dioxide inhalation. After transition to air, alveolar  $P_{CO_2}$  dropped significantly below the initial level in eight subjects and was considered an after-effect of central excitation. The effect was greater after 5 percent, suggesting that 7 percent has a narcotic effect, commensurate with the direct stimulatory effect on the respiratory center. A group of trained instructors at the escape training tank, who had previously shown significantly lower respiratory responses to low oxygen than a group of laboratory personnel, also showed a significantly lower respiratory response to the carbon dioxide mixtures, suggesting that the differences in response to carbon dioxide and low oxygen are based on different sensitivity of the chemoreceptors. However, adaptation to low oxygen and high carbon dioxide, with a resulting change in the centrogenic drive of breathing, might take place. Tests of ventilatory response to high carbon dioxide as well as low oxygen, were considered as a physiological selection device for underwater swimmers. Norins, Schroeder, Grodins, Gray and Jones (1954) 1953, have pointed out that there is considerable evidence in the literature indicating that ventilation is a positive linear function of arterial  $P_{CO_2}$  during the steady state of carbon dioxide inhalation in man. There is other evidence however, indicating that this relationship does not hold in the transient states following either the initiation or termination of carbon dioxide inhalation. Various qualitative explanations of this transient association between ventilation and arterial  $P_{CO_2}$  have been suggested, but none have been adequately explored according to the authors. In their analysis

they investigated the implications of a hypothesis assigning the effective controlling carbon dioxide concentration to tissues rather than to arterial blood. That very high concentrations of carbon dioxide are actually depressant to respiration in the human being has been confirmed by the studies of Stroud, Ewing and Mack (1973) 1953. These authors studied the effects of inhalation of 30 percent carbon dioxide in oxygen on alveolar  $P_{CO_2}$ , the respiratory minute volume, respiratory rate and tidal volume, in a young female psychiatric patient. The average result of eight exposures for 2–2.75 minutes were as follows: The  $P_{CO_2}$  rose rapidly from 35 to 205 mm. Hg within a minute, and remained almost constant during carbon dioxide inhalation. The respiratory rate curve followed the  $P_{aCO_2}$  closely increasing from 15 to 35. The respiratory minute volume rose more slowly from 11 to 36 liters in 1.25 minutes, and then fell steadily to 29 liters at 2 minutes. The tidal volume changes paralleled those of respiratory minute volume, with values of 0.85, 1.0 and 0.80 liters, respectively. Unconsciousness occurred within one minute. Following the abrupt return to air breathing, the  $P_{CO_2}$  fell to 43 mm. Hg within one minute, and then to 39 mm. Hg in 4.5 minutes. Respiratory minute volume rose from 20 to 30 liters in 1.25 minutes after withdrawal of carbon dioxide, and then declined to 16 liters in 4.5 minutes. The corresponding values for respiratory rate were 28, 30 and 18. Those for tidal volume were 0.70, 0.90 and 0.90 liters. Convulsive phenomena occurred or were accentuated during the most rapid change in  $P_{CO_2}$ . Consciousness was regained after about three minutes of air breathing. Chapin (1901) 1954, and (1902) 1955, has studied the ventilatory response of unrestrained and unanesthetized hamsters to carbon dioxide. The chamber containing these animals was ventilated with 3–35 percent carbon dioxide and 20 percent oxygen in nitrogen at the rate of five liters per minute for 20–30 minutes (a time calculated to achieve a steady state). Each experiment was preceded by a 20 to 30 minute control run. The resting respiratory rate showed an inverse ratio with body weight and a direct ratio with tidal volume and minute volume. Breathing carbon dioxide increased the rate more than the tidal volume. The peak ventilation oc-

curred when the inspired gas mixture contained 20 percent carbon dioxide in 20 percent oxygen and 60 percent nitrogen, and at this level there was an approximately 6.6 fold increase in the ventilatory ratio.

In a review of reflex control of airway calibre, Widdicombe (1079) 1962, has drawn attention to the finding that in animals breathing high carbon dioxide mixtures results in bronchial spasm, and that this effect depends upon the intact vagus nerve. This bronchial constriction has been reported also by Daly, Lambertsen and Schweitzer (1011) 1952; by Peters (1057) 1955; and by Whittenberger (1078) 1962.

According to Forster (1021) 1962, the diffusion capacity of the lungs is increased 24.5 percent in dogs breathing 7.5 percent carbon dioxide for 5–10 minutes. Increased breathing resistance favors carbon dioxide retention and therefore decreases sensitivity to carbon dioxide (Lanphier (1041) 1958). In Lanphier's studies it was found that subjects breathing nitrogen-oxygen revealed absent or minimal carbon dioxide retention. The degree to which subjects retained carbon dioxide varies and there is a relationship between this tendency and their ventilatory response to carbon dioxide. The author favors abandoning nitrogen-oxygen mixtures in favor of helium-oxygen mixtures for mixed-gas SCUBA diving. These results have been verified by Eldridge and Davis (1020) 1959. With increasing resistance these authors found that the  $P_{CO_2}$  and work, rose in parallel, whereas ventilation remained constant or even decreased. In the presence of a constant carbon dioxide stimulus, increasing airway resistance caused a progressive decrease in the ventilatory response to carbon dioxide. The maximum breathing capacity was not in itself the limiting factor in the ventilatory response to carbon dioxide. It was concluded that the mechanical abnormalities of the respiratory apparatus are important factors in reducing the ventilatory response to carbon dioxide, and that work of breathing is a more satisfactory index of respiratory stimulation than ventilation. Since patients with obstructive emphysema have non-elastic resistance values in the same range as those used in this study, it was concluded that the low ventilatory response to carbon dioxide in

these patients can in large part be explained by the mechanical abnormalities. For further consideration of the effect of respiratory tract obstruction upon the ventilatory response to inhaled carbon dioxide, a report by Samet, Fierer and Bernstein (1064) 1960, should be consulted. The linear part of the carbon dioxide response curve has been shown to be an inverse function of alveolar oxygen pressure. This has been confirmed by Lloyd, Jukes and Cunningham (1046) 1958. This has likewise been demonstrated by Lambertsen, Hall, Wollman and Goodman (1037) 1963, using two atmospheres of oxygen and 0.2 atmospheres of oxygen. The authors pose an important question: does high oxygen deactivate chemically the peripheral arterial chemoreceptors, even blocking the stimulatory influences of increased  $P_{CO_2}$ . It may be that anoxia and increased carbon dioxide effect the same sensors.

There are age differences in carbon dioxide sensitivity. Cross, Hooper and Oppe (1009) 1953, and Avery, Chernick, Dutton and Permutt (992) 1963, have shown that infants are more sensitive to carbon dioxide than adults. On the other hand, Bour and Blimet (997) 1961, found that healthy aged subjects showed a normal sensitivity to carbon dioxide, as compared with healthy young adults, but that there was a decrease in the respiratory sensitivity to carbon dioxide in patients with respiratory insufficiency.

In general, hypothermia diminishes the respiratory response of increased carbon dioxide and hyperthermia increases the response. Pertinent reports have been given by Cunningham and O'Riordan (1010) 1957; by Salzano and Hall (1063) 1960; by Albers (986) 1961; and by Kilmore and Chase (1034) 1962.

Patients with obstructive emphysema reveal a diminished ventilatory response to carbon dioxide. For papers dealing with this subject the reader should consult the following: Prime and Westlake (1058) 1954; Alexander, West, Wood and Richards (988) 1955; Cherniack and Snidal (1003) 1956; Fritts, Fishman and Cournand (1022) 1957; Richards, Fritts and Davis (1061) 1958; and Brodovsky, MacDonnell and Cherniack (999) 1960.



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### G. METABOLISM

For a general review of the subject of tissue buffering the reader is referred to a paper on carbon dioxide and intracellular homeostasis by Fenn (1084) 1961. Johnson and Schaefer (1088) 1955, have reported a study of plasma, whole blood, liver and muscle electrolytes during carbon dioxide retention and recovery. During exposure of guinea pigs to 15 percent carbon dioxide, three phases of electrolyte changes are observed. An initial 24 hour period of hemoconcentration and uncompensated respiratory acidosis is succeeded by a transient hemodilution during the next two days. As indicated by rising blood pH, the acidosis becomes compensated after 24 hours of exposure. Hematocrit values return to normal during the fourth and seventh day of exposure. Both plasma and whole blood water content reflect this pattern. These changes are accompanied by an initial sharp rise in carbon dioxide tension in whole blood, with a continued more gradual rise throughout exposure. Tissue water remains relatively constant during these shifts in concentration of extracellular fluid. During the period of acute uncompensated acidosis there is a pronounced fall in blood potassium concentration, while sodium in whole blood and plasma rises slightly. Simultaneously, sodium concentration of liver and striated muscle increases but returns to normal during the period of compensated acidosis. Blood chloride shows little change during the acute phase, but decreases during the period of compensation. Tissue phosphorus increases sharply during the first 24 hours under carbon dioxide and remains high during the phase of compensation while blood and plasma phosphorus decreases. During recovery periods up to 12 days after exposure, certain of the tissue electrolytes return towards normal only gradually. Liver and muscle phosphorus

remained below control values. In acidosis produced by administering 6 percent carbon dioxide to dogs, Robin (1099) 1963, reported a change of 0.35 pH units in extracellular water accompanied by an 0.23 pH unit change in intracellular water. The bicarbonate ion showed corresponding changes in both compartments. Elkin-ton, Singer, Barker and Clark (1083) 1955, have reported studies in man of the effects of acute experimental respiratory alkalosis and acidosis on ionic transfers in total body fluids. Ionic transfers between the extracellular fluid (assumed to be 20 percent of body weight with changes estimated on the basis of the chloride space) and the intracellular fluid were calculated in normal subjects during and after acute respiratory alkalosis produced by hyperventilation. In another group of human subjects the same transfers were calculated during and after respiratory acidosis produced by carbon dioxide inhalation. Direct calculations were made of sodium and potassium transfers, as well as indirect calculations of intracellular hydrogen on the basis of changes in bicarbonate and other buffer anions in the extracellular fluid and red cells. In respiratory alkalosis the authors found that hydrogen left the cells and sodium entered the cells. In respiratory acidosis, hydrogen tended to enter, and sodium to leave the cells; but these mean changes were not quite significant at the five level. In both types of experiments the sums of hydrogen transfer in one direction, and of sodium in the other, were highly significant. The ratio of hydrogen transfer to sodium transfer in the opposite direction was approximately two to one under these conditions. A one to one transfer of anion with that of hydrogen not exchanged for sodium appeared to be involved. In both types of experiments the changes in cell potassium were much smaller in magnitude, or were negligible, for the short duration of the stimuli. The authors concluded that in acute respiratory acid-base disturbances a large part of the immediate buffering of the extracellular fluid is achieved by exchanges of hydrogen for sodium across the cell boundaries in body tissues.

Thompson and Brown (1105) 1957, and (1106) 1960, have studied the tissue carbon dioxide concentrations in hypercapnic rats. As part of an investigation of the chemical changes in



tissues resulting from hypercapnia post-mortem, tissue carbon dioxide concentrations were measured in the rat following exposure of the live animal to high concentrations of carbon dioxide. The tissue was rapidly frozen in liquid nitrogen, ground and transferred to 1.0 N sodium hydroxide. It was then digested at 60° C. and the carbon dioxide determined by a modified Van Slyke technique. Control values in the skeletal muscle averaged 13.2 mM. of carbon dioxide/Kg wet tissue. Following exposure to 30 percent carbon dioxide in 70 percent oxygen for one hour the skeletal muscle carbon dioxide concentration averaged 29.2. Serial changes in tissue carbon dioxide content during acute respiratory acidosis have been investigated by Nichols (1096) 1958. Male albino rats were exposed to 24 percent carbon dioxide in air for periods ranging from one half to 24 hours, and the pH and carbon dioxide of blood and tissues compared with control rats. A profound respiratory acidosis with high plasma carbon dioxide and a plasma pH of 6.92 appeared after one half hour of exposure, followed after 7–15 hours by a further slow rise in plasma carbon dioxide and a rising pH which reached 7.10 after 48 hours. The total carbon dioxide content of muscle and brain rose rapidly but reached a plateau after five hours. The rate of rise, and the absolute level of tissues carbon dioxide was higher in the brain than in muscle. In contrast to other tissues, the bone carbon dioxide content remained fixed or declined slightly, even after 48 hours of exposure. The author concluded that soft tissues rather than bone form the site of storage of carbon dioxide under conditions of these experiments. In the experiments of Levitin, Jockers and Epstein (1093) 1958, female rats were subjected to 8 percent carbon dioxide for 24 hours and compared with controls kept in room air. Immediately after removal from the carbon dioxide chamber the animals were sacrificed by exsanguination and specimens of liver, bone and muscle obtained for analysis. Exposure to carbon dioxide caused elevation of plasma carbon dioxide content and a decrease in plasma chloride. The plasma sodium remained unchanged and plasma potassium was slightly but significantly elevated. There were no differences between the experimental and control groups in water and

fat content of liver, bone and muscle. Experimental and control groups were not differentiated in terms of sodium content of liver, bone or muscle. There was no difference in calcium. Muscle potassium of rats in carbon dioxide chamber decreased significantly while bone potassium remained similar to control values. These results differ from those of previous workers, possibly because the short duration of the present experiments avoided certain metabolic effects which complicate long-term studies of experimental respiratory acidosis. The data suggest to the authors that potassium proteinate of muscle is capable of buffering carbonic acid as well as strong acids, but that combinations of sodium with carbonate in bone, although capable of buffering metabolic acidosis, cannot serve as an effective buffer for carbonic acid.

Katzman, Villee and Beecher (1089) 1953, have found that when bicarbonate concentration was kept constant rat and dog tissues incubated at 10, 15 and 20 percent carbon dioxide production of lactic acid was less than when duplicate tissues were incubated at five percent carbon dioxide. This change in lactic acid production is reversed if the Krebs cycle is inhibited by malonate or arsenite. If the pH is kept constant at 7.4, rat and dog tissues incubated at 10, 15 and 20 percent carbon dioxide produce more lactic acid than to duplicate tissues incubated at five percent carbon dioxide. At a pH 6.8–7.1 this effect is diminished or absent. Human tissue, like rat and dog tissue, shows an increased production of lactic acid in an iso-pH system as the carbon dioxide concentration is increased, and a decreased production of lactic acid in an isobicarbonate system at carbon dioxide concentrations of 15 and 20 percent. The serum calcium response was cyclic, rising from 10.02 mg. percent to 11.06 mg. percent after the second day, falling to 9.84 in the third day, rising to 11.20 on the fifth and 11.55 on the sixth, and began decreasing on the seventh day. The values between the seventh and fifteenth days were not measured but on the last day of this period the calcium was 10.30 mg. percent. Serum inorganic phosphate changes inversely parallel to calcium changes through the sixth day when a fall in phosphate becomes precipitous to 5.1 mg. percent (control value 9.85 mg. percent). The au-

thors suggest that the second and sixth day peaks were accounted for by parathyroid stimulation.

The hyperglycemic response to carbon dioxide has been reported by King, Williams and Schaefer (1092) 1954. These authors made total blood sugar determinations from the tail vein blood of normal, adrenalectomized and hypophysectomized rats of the Wistar-Hisaw strain ( $70 \pm 10$  days of age). These determinations were carried out before exposure, during exposure at intervals of 10, 30 and 60 minutes, and one hour after exposure to 30 percent carbon dioxide in air and in oxygen. In the normal rats the blood sugar increased 60 percent over the normal after one hour exposure to 30 percent carbon dioxide in air, and increased 30 percent after one hour exposure to 30 percent carbon dioxide in oxygen. The blood sugars returned to normal one hour after exposure. Neither adrenalectomy nor hypophysectomy muscle composition in respiratory acidosis a paper by Cooke, Coughlin and Segar (1081) 1952, may be consulted. Male albino rats were exposed to an atmosphere: a) containing 11 percent carbon dioxide for two weeks, and b) containing 13 percent carbon dioxide for three weeks. Oxygen concentrations did not fall below 17 percent. Temperature was maintained at  $23^{\circ}\text{C}$ . and relative humidity at 80 percent. Rats were removed from the chamber for 20 minutes every third day for cleaning, etc. After periods of exposure animals were anesthetized with ether within one to three minutes after removal from the chamber. Bicarbonate, pH and carbonic acid were not determined. Changes in serum were characteristic of chronic respiratory acidosis as follows: high serum bicarbonate (41 mM/l) and low serum chloride (85 mM/l). Muscle potassium content was at an upper limit of normal, namely 48 mM/100 gms. of fat-free solids. Intracellular sodium was somewhat reduced, namely 2.2 mM/100 gms. of fat-free solids. These results are in striking contrast to those of metabolic acidosis in which serum bicarbonate is high and serum chloride low. Rises in serum calcium have been shown by Stanmeyer, King, Scofield and Colby (1104) 1962, to result from exposure to carbon dioxide. Histological examination of

the dentin of the incisor tooth of rats exposed to 15 percent carbon dioxide and 21 percent oxygen for 1-15 days (plus 7 days with 7 days recovery, and 14 days with 14 days recovery) showed an accentuation of the incremental calcification pattern and vascular inclusions. The dentin matrix was formed at the same rate as in control animals. The experimental animals tended to lose weight and those allowed to recover showed a weight gain during the recovery completely eliminated the hyperglycemic response to 30 percent carbon dioxide in air or in oxygen. As in the normal animal, the response was less under 30 percent carbon dioxide in oxygen than in air. These results correlate with the findings of previous workers. King (1091) 1957, exposed normal and adrenalectomized mature male rats of the Wistar-Hisaw strain to an atmosphere of 30 percent carbon dioxide in oxygen for periods up to five hours. Epinephrine hydrochloride was injected subcutaneously just prior to exposure at a dose level of 0.02 mg./100 gm. of body weight. Liver, muscle glycogen and blood sugar determinations were carried out one, two, three, four and five hours after injection. In the normal rats narcotized with carbon dioxide, epinephrine effects neither the muscle glycogen stores nor the carbon dioxide-evoked hyperglycemia, but prevents the cyclic reaccumulation of liver glycogen observed under conditions of carbon dioxide narcosis alone. In the adrenalectomized rats epinephrine does not change the lowering of liver glycogen produced by high concentrations of carbon dioxide but reverses the previously observed hypoglycemia to hyperglycemia at the apparent further expense of glycogen stores in the muscle which are practically depleted. These studies indicated to the author that epinephrine inhibits the reaccumulation of liver glycogen which occurs in rats under conditions of carbon dioxide narcosis.

Regarding the effect of exposure of carbon dioxide on oxygen consumption, Killion and Schaefer (1090) 1953, studied cellular oxidation in liver tissue slices of guinea pigs and rats exposed to 1.5 percent carbon dioxide for periods from 1 to 41 days. No significant changes in oxidation were found, as measured by the oxygen consumption of liver tissue slices. Similar studies have been conducted by Stamm



(1103) 1960, who investigated *in vitro* influence of carbon dioxide on the metabolism of lung and liver tissues. At carbon dioxide concentrations of 2.5–13 percent, the oxygen uptake of lung tissue remained practically the same, whereas that of the liver was reduced. The effect on liver slices was greatest in the 13 percent carbon dioxide and least in the 2.5 percent carbon dioxide. Significantly, with a carbon dioxide concentration of 13 percent a considerable reduction of liver metabolism occurred. With the lower carbon dioxide concentration of 2.5 percent the metabolism was likewise reduced, but less than in the case of the 13 percent concentration.

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## H. ENDOCRINES

It appears from a paper by Tenney (1123) 1960, that critical concentrations of carbon dioxide are essential for optimum synthesis of acetylcholine. This action is apparently specific. Carbon dioxide also enhances the excitability of sympathetic fibers to electrical stimulation. Higher concentrations of carbon dioxide initiate release of catecholamines from the renal medulla. Studies by the author lead to the conclusion that the sympathetico-adrenal response to carbon dioxide is determined solely by an  $H^+$  effect. There is a direct relation between the carbon dioxide concentration of the blood and hydrochloric acid secretion by the stomach. Carbon dioxide also invariably increases the salivary flow in the dog.

According to Johnson and Bean (1114) 1955, carbon dioxide augments pulmonary damage produced by oxygen under high pressure. Sympathetic blockage prevents this augmentation, as well as damage by high pressure oxygen itself. This augmentation by carbon dioxide, that of pulmonary effects of oxygen under high pressure itself, is in large measure mediated through the sympathetics and adrenals and possibly the hypothalamus. King, Williams, Mego and Schaefer (1116) 1954, exposed normal and hypophysectomized rats to 1.5 percent carbon dioxide for 42 days. Both groups of animals revealed a notable eosinopenia and lymphopenia, correlated with a drop in adrenal cholesterol and ascorbic acid. The blood sugar was maintained at a normal level, apparently at the expense of liver and muscle glycogen stores. During this period of exposure to carbon dioxide adrenal cortical activity was increased and had not returned to pre-stimulation levels when the animals were sacrificed at intervals during a ten day recovery period in normal air. Results of the blood and adrenal studies indicated to the authors that prolonged exposure to 1.5 percent carbon dioxide causes a stress on the pituitary-adrenal system which is not reversed during a ten day recovery period. Similar results have been reported by King (1115) 1962.

In dogs, Richards (1120) 1956, found maximal adrenocortical stimulation in all animals exposed to 20 percent carbon dioxide, a response which

persisted for as long as four hours. This adrenocortical response was abolished by hypophysectomy. Barcroft, Basnayake, Celander, Cobbold, Cunningham, Jukes and Young (1110) 1957, concluded in human studies that carbon dioxide enhanced the respiratory response to norepinephrine. According to Cross and Silver (1112) 1962, hypercapnia in rabbits (80 percent carbon dioxide and 20 percent oxygen) for 5 to 15 seconds induced a sympathetic discharge resembling that obtained from hypothalamic stimulation. These effects were reversibly blocked by thorocolumbar spinal anesthesia. The response elicited by hypercapnia was not impaired by discrete bilateral lesions in the septum, hippocampus and medial thalamus. Hypothalamic lesions on the other hand often reduced and occasionally prevented the central discharge. Manley and Woodbury (1119) 1964, found that dogs ventilated with 15 percent carbon dioxide in oxygen showed a significant reduction of positive chronotropic response to 2  $\mu\text{g}/\text{Kg}$  epinephrine within a ten minute hypercapnic period. When 30 percent carbon dioxide was used the positive chronotropic response was virtually eliminated and the positive inotropic response was reduced. Pretreatment with phentolamine (6.25  $\text{mg}/\text{Kg}$ ) provided marked potentiation of the blocking effects caused by carbon dioxide. Equivalent cardiac stimulation elicited by acetylcholine (500  $\mu\text{g}/\text{Kg}$ ) given to the atropinized dogs was unaltered during a ten minute hypercapnic period induced by inhalation of 30 percent carbon dioxide. The effect of hypercapnia upon epinephrine-induced cardiac stimulation was also investigated in dogs pretreated with atropine, chlorisondamine (P-286), acute bilateral adrenalectomy or reserpine. These treatments under the experimental conditions of the authors caused no reduction of the positive chronotropic response to epinephrine and produced only minor alterations in the positive inotropic response. Reduction of the pressor response to epinephrine by hypercapnia was found to be significantly less in those animals which had experienced a reduction of available catecholamine stores.

Schaefer, King, Mego and Williams (1121) 1954, have reported in normal male guinea pigs exposed to 1.5 percent carbon dioxide over



periods of 42 days and 91 days that there is an initial decrease in body weight lasting for 13 days followed by an increase. After a latent period of seven days adrenal cortical activity increased during exposure to 1.5 percent carbon dioxide as indicated by a decrease in adrenal cholesterol content and notable eosinopenia and lymphopenia. The blood sugar did not change while liver glycogen and muscle glycogen decreased significantly during exposure to the carbon dioxide. Erythrocytes, hemoglobin and hematocrit increased during carbon dioxide exposure after a latent period of seven days. The observed rise in the reticulocyte counts indicate a slight erythropoietic stimulation. A further paper by Tenney (1122) 1956, may be consulted for evidence that carbon dioxide serves as a potent stimulus to increase the titer of circulating sympathetico-adrenal catecholamines in the cat.

Chen, Sabel and Lyons (1111) 1963, found in experiments on human subjects that the ventilatory response to four and six percent carbon dioxide inhalation in air was increased by administration of progesterone.

Johnson and Bean (1114) 1955, have pointed out that although it is well known that a small increase of carbon dioxide augments most toxic reactions to oxygen under high pressure, information concerning influence on lung damage in oxygen under high pressure is deficient. Experiments on adult albino rats exposed to OHP as well as animals exposed to OHP plus carbon dioxide (40 mm. Hg partial pressure) showed that carbon dioxide enhances lung damage induced by OHP. Earlier work of these authors indicated that the sympathetico-adrenal system contributes importantly to lung damage in OHP and to ascertain whether the carbon dioxide enhancement of OHP lung damage might be due to sympathetic involvement. Test rats were injected with a sympatholytic agent, SKF501 (10 mg/Kg) and a control group with a saline blank were exposed in pairs to OHP plus carbon dioxide (80 mm. Hg). Some rats injected with SKF501 were used as air controls. All saline injected oxygen controls showed gross lung damage and most succumbed whereas only 12 percent SKF injected oxygen exposed animals showed comparable lung damage although 50 percent succumbed. Several SKF501 animals in OHP

showed small patches of hemorrhage but lung weight was unchanged, in contrast to a 250 percent lung weight increase in saline controls. The data indicate that carbon dioxide augments pulmonary damage by OHP and that sympathetic blockage protects against this augmentation as well as against the damage by OHP itself. This augmentation by carbon dioxide, like that of the pulmonary effect of OHP itself is in large measure mediated through the sympathetico-adrenal system and possibly through the hypothalamus. Tenney (1122) 1956 has pointed out that carbon dioxide serves as a potent stimulus to increase the titer of circulating sympathetico-adrenal catechol amines in the cat. In man Barcroft, Basnayake, Celandier, Cobbold, Cunningham, Jukes and Young (1110) 1957, have demonstrated an enhancing effect of carbon dioxide on the respiratory response to nor-epinephrine. Administration of 10 ug. of nor-epinephrine per minute for 15 minutes to human subjects breathing carbon dioxide and air mixtures was carried out. The carbon dioxide percentage varied from two to five percent. A sustained increase of 20–50 percent in pulmonary ventilation was obtained in spite of a small fall in alveolar  $P_{CO_2}$  which accompanied hyperpnea. At alveolar  $P_{CO_2}$  tensions of around 43 mm. Hg ventilation was increased by about 10 L/min. by infusion of nor-epinephrine.

The reader should consult a paper by Tenney (1123) 1960, on the effect of carbon dioxide on neurohumoral and endocrine mechanisms. Critical concentrations of carbon dioxide appear to be essential for optimal synthesis of acetylcholine. With regard to the sympathetic nervous system and the adrenal medulla there is also evidence that carbon dioxide actually enhances the excitability of sympathetic fibers to electrical stimuli. Higher concentrations of carbon dioxide initiate the release of catecholamines from the adrenal medulla. The role of carbon dioxide in certain aspects of adrenal function have been demonstrated by King (1115) 1962.

Adult male rats were exposed for 10 and 30 minutes as well as one, two, three and four hours to 30 percent carbon dioxide and a reduction was found in adrenal cortical ascorbic acid ranging from 500 mg. percent to 280 at 10 and 30 minutes and 320 mg. percent at one hour. In

rabbits under urethane anesthesia Cross and Silver (1112) 1962, found that hypercapnia induced by inhalation of a mixture of 80 percent carbon dioxide and 20 percent oxygen for from 5–15 seconds, produced a sympathetic discharge resembling that from hypothalamic stimulation. The effect was similar to that of hypoxia, but the hypercapnia was more potent than the hypoxia. The effects were reversibly blocked by thorolumbar spinal anesthesia. Placements of discrete bilateral lesions in the septum, hippocampus and medial thalamus did not impair the sympathetic activity elicited by hypercapnia. Hypothalamic lesions on the other hand often reduced and occasionally prevented the central sympathetic discharge. Epinephrine-induced cardiac stimulation had been blocked by carbon dioxide inhalation in studies on dogs carried out by Manley and Woodbury (1119) 1964. Dogs were ventilated with 15 percent carbon dioxide and demonstrated a significant reduction of positive chronotropic response to 2 ug./Kg. of epinephrine within ten minutes after carbon dioxide inhalations started. When 30 percent carbon dioxide was employed the positive chronotropic response was almost entirely eliminated and the positive inotropic response reduced. The effect of hypercapnia upon epinephrine-induced cardiac stimulation has also been investigated in dogs pretreated with atropine, acute bilateral adrenalectomy or reserpine. These treatments under the experimental conditions of the authors caused no reduction of the positive chronotropic response to epinephrine and produced only minor alteration of the positive inotropic response. Reduction of the pressor response to epinephrine by hypercapnia was found to be significantly less in those animals which had experienced a reduction of available catecholamine stores.

In male guinea pigs the effects of prolonged exposure to 1.5 percent carbon dioxide in air for periods up to 91 days have been studied by Schaefer, King, Mego and Williams (1121) 1954. In two experiments normal male guinea pigs, Connaught strain, were exposed to 1.5 percent carbon dioxide over periods of 42 days and 91 days. The carbon dioxide tension in the blood rose significantly and the pH dropped slightly during exposure to carbon dioxide. Body weight showed a biphasic change, an initial de-

crease lasting for a period of 13 days followed by an increase. After a latent period of seven days adrenal cortical activity was found to be increased during exposure to 1.5 percent carbon dioxide as indicated by a decrease in adrenal cholesterol content and marked eosinopenia and lymphopenia. Blood sugar did not change, while liver glycogen and muscle glycogen decreased significantly during exposure to carbon dioxide. Erythrocytes, hemoglobin and hematocrit increased during carbon dioxide exposure after a latent time of seven days. The observed rise in the reticulocyte counts indicated a slight erythropoietic stimulation. The increased activity of the adrenal-pituitary system found during exposure to 1.5 percent carbon dioxide may play a role in the loss of body weight since stimulation of the adrenal medulla with epinephrine release enhances the metabolic rate.

A study of the effect of carbon dioxide exposure on adrenal 17-hydroxycorticosteroid secretion in dogs has been reported by Richards (1120) 1956. Male mongrel dogs with polyethylene cannulas in the right adrenal vein and carotid artery were placed in a recompression chamber at atmospheric pressure. Oxygen and carbon dioxide content of the chamber were measured by continuous sampling through a Beckman oxygen analyzer and a Liston-Becker infrared carbon dioxide analyzer. Following a control period of 30 minutes during which adrenal venous and arterial blood samples were collected, the dogs were subjected to various concentrations of carbon dioxide in air. Experiments were divided into the following groups: unanesthetized dogs exposed to 2.5, 5 and 10 percent carbon dioxide for periods of one hour each; anesthetized dogs exposed to 2.5, 5 and 10 percent carbon dioxide for one hour each; 10, 20 and 30 percent carbon dioxide for one hour each; 20 percent carbon dioxide for four hours; and anesthetized hypophysectomized dogs exposed to 20 percent carbon dioxide for three hours. Intermittent arterial and venous blood samples were obtained during the carbon dioxide exposure periods. Adrenal venous bloods were analyzed for 17-hydroxycorticosteroids. Arterial bloods were collected under oil and analyzed for pH, carbon dioxide content and in some cases for oxygen content. Adrenocortical stimulation



was correlated with decreased pH and increased carbon dioxide content in the arterial blood. Maximal adrenocortical stimulation occurred in all dogs exposed to 20 percent carbon dioxide and this response persisted for as long as four hours. Hypophysectomy abolished the adrenocortical response to carbon dioxide exposure.

King, Williams, Mego and Schaefer (1116) 1954, exposed normal and hypophysectomized rats to 1.5 percent carbon dioxide for 42 days. Both groups of animals demonstrated a marked eosinopenia and lymphopenia, correlated with a drop in adrenal cholesterol and ascorbic acid. The blood sugar was maintained at a normal level, apparently at the expense of liver and muscle glycogen stores. During this exposure to carbon dioxide adrenal cortical activity was increased and had not returned to initial levels when the animals were sacrificed at intervals during a ten day recovery period in normal air. The results of the blood and adrenal studies indicate that prolonged exposure to 1.5 percent carbon dioxide produces a stress on the pituitary-adrenal system which is not reversed during a ten day recovery period.

1110. Barcroft, H., V. Basnayake, O. Celander, A. F. Cobbold, D. J. C. Cunningham, M. G. M. Jukes and I. M. Young. The effect of carbon dioxide on the respiratory response to noradrenaline in man. *J. Physiol.*, 1957, 137: 365-373.

1111. Chen, H. C., B. Savel and H. A. Lyons. CO<sub>2</sub> response curves after administration of progesterone and NaHCO<sub>3</sub>. *Fed. Proc.*, 1963, 22: 221.

1112. Cross, B. A. and L. A. Silver. Central activation of the sympathico-adrenal system by hypoxia and hypercapnia. *J. Endocrin.*, 1962, 24: 91-103.

1113. Hamolsky, M. W. and M. Stein. Effects of 2-amino-2-hydroxy-methyl-1, 3-propane-diol, pCO<sub>2</sub>, and pH on plasma protein binding of the thyroid hormones. *Ann. N. Y. Acad. Sci.*, 1961, 92: 528-538.

1114. Johnson, P. C. and J. W. Bean. Carbon dioxide and the sympathoadrenal system in O<sub>2</sub> at high pressure (OHP). *Fed. Proc.*, 1955, 14: 81.

1115. King, C. T. G. Carbon dioxide and certain aspects of adrenal function. pp. 117-126 in: *Man's dependence on the earthly atmosphere*. Edited by K. E. Schaefer. The MacMillan Company, New York, 1962, 416 pp.

1116. King, C. T. G., E. E. Williams, J. L. Mego and K. E. Schaefer. Effects of prolonged exposure to carbon dioxide in air on pituitary-adrenal interrelations in the male albino rat. U.S. Navy. Submarine base, New London, Conn. Medical research laboratory. *Project NM 002 015.11*, Rept. no. 3, 16 March 1954.

1117. Langley, L. L., P. W. Skokel and E. J. Moore. Role of hypoglycemia and carbon dioxide in the reaction to stress. *Endocrinology*, 1954, 54: 425-430.

1118. Loomis, W. F. *Sexual differentiation in Hydra*; control by carbon dioxide tension. *Science*, 1957, 126: 735-739.

1119. Manley, E. S., Jr. and R. A. Woodbury. Blockade of epinephrine-induced cardiac stimulation by carbon dioxide inhalation. *Fed. Proc.*, 1964, 23: 125.

1120. Richards, J. B. and S. N. Stein. Effect of carbon dioxide exposure on adrenal 17-hydroxycorticosteroid secretion in dogs. *Fed. Proc.*, 1956, 15: 151.

1121. Schaefer, K. E., C. T. G. King, J. L. Mego and E. E. Williams. Effects of prolonged exposure to 1.5% carbon dioxide in air for periods up to 91 days on body weight, carbohydrate metabolism, and adrenal cortical activity in guinea pigs. U. S. Navy. Submarine base, New London, Conn. Medical research laboratory. *Project NM 002 015.11.05*, 12 October 1954, 21 pp.

1122. Tenney, S. M. Sympatho-adrenal stimulation by carbon dioxide and the inhibitory effect of carbonic acid on epinephrine response. *Amer. J. Physiol.*, 1956, 187: 341-346.

1123. Tenney, S. M. The effect of carbon dioxide on neurohumoral and endocrine mechanisms. *Anesthesiology*, 1960, 21: 674-685.

## I. SWEATING

Inhalation of carbon dioxide causes an increase of sweating as shown by Bullard (1124) 1964. The inhalation of six percent carbon dioxide by male subjects exposed to three ambient room temperatures gave an increase of sweating as measured by resistance hygrometry. The increase reached approximately 100 percent over control levels. All measured body temperatures were reduced during or following the carbon dioxide exposure. In the recovery a striking reduction of sweating occurred which ended as the skin temperature rose.

1124. Bullard, R. W. The effects of carbon dioxide inhalation on sweating. *J. appl. Physiol.*, 1964, 19: 137-141.

## J. KIDNEY

For a general discussion of the effect of carbon dioxide on the kidney, a paper by Kennedy (1135) 1960, may be consulted. Electrolyte changes under carbon dioxide have been reported by Nichols and Schaefer (1140) 1962. Data on rats exposed to 24 percent carbon dioxide in air from 30 minutes to 48 hours indicate the rapid development of respiratory acidosis within 30 minutes. Hypercapnia in dogs causes an immediate increase in bicarbonate reabsorption by the kidneys irrespective of pH changes. In man after

30 minutes of 7 percent carbon dioxide inhalation, urinary pH falls, titratable acid and hydrogen ion increases, and phosphate and chloride ion increases. Potassium secretion falls, ammonium ion increases a small but significant amount and sodium excretion increases.

Breathing carbon dioxide leads to a rise in urine flow. Barbour, Bull, Evans, Jones and Logothetopoulos (1126) 1953, found that breathing 5-7 percent carbon dioxide causes a marked increase in urine flow in the recumbent normal subject, but no regular change in the sitting subject. During the diuresis induced by carbon dioxide, urine specific gravity falls and there is a slight rise in the excretion of total moles per minute. Urea contributes most of this increase and there is no significant change in the excretion per minute of creatinine, sodium, chloride or potassium. The glomerular filtration rate and renal plasma flow are not altered. The diuresis ordinarily induced by carbon dioxide can be inhibited by pitressin. The freezing point of plasma is not significantly altered by breathing carbon dioxide. Thus haemodilution is not considered by the authors to be responsible for the diuresis. In fact, the diuresis may persist despite hemoconcentration. The probable mechanism of the carbon dioxide diuresis, according to the authors, is an inhibition of pitressin release. Currie and Ullmann (1130) 1961, also called attention to increased urine flow associated with carbon dioxide inhalation. According to Valtin, Wilson and Tenney (1151) 1959, carbon dioxide is probably mediated via nonosmotic influences on the supra-opticohypophyseal system. Since the left atrial stretch receptor mechanism is one such nonosmotic system which carbon dioxide might influence, experiments were designed by the authors to elucidate its role. It was found that carbon dioxide diuresis may be abolished by erect posture or by applying tourniquets high on the thighs while supine, and that it may be restored by standing in a tank of water or by mild exercise. Increases in plasma volume, total blood volume, or pulmonary blood volume, which conceivably might stretch the left atrium, did not occur during the carbon dioxide diuresis. Voluntary hyperventilation mimicking that which accompanies carbon dioxide inhalation resulted in a much smaller diuresis and one

which unlike that of carbon dioxide was accompanied by increased sodium excretion. Maintaining normal alveolar  $P_{CO_2}$  during voluntary hyperventilation by simultaneous inhalation of two percent carbon dioxide in no way altered this result. Bilateral vagus section in animals does not abolish carbon dioxide diuresis, but may enhance it. It was concluded by the authors, therefore, that the left atrial stretch receptor mechanism is not the afferent system for carbon dioxide diuresis.

In a study of the effect of prolonged exposure to carbon dioxide, 20 subjects were exposed to 1.5 percent carbon dioxide for 42 days, by Nichols, Schaefer and Carey (1141) in 1957. This exposure resulted in a slight uncompensated respiratory acidosis which lasted for 23 days and was followed by compensatory respiratory acidosis. The red cells exhibited an increased sodium content and commensurately decreased potassium content during exposure to carbon dioxide and during nine days of recovery in air. Caloric intake decreased during exposure. Sodium balance studies showed a biphasic pattern, retention during the phase of uncompensated respiratory acidosis, followed by an increased excretion during the phase of compensated respiratory acidosis, and during the nine day recovery period on air. The potassium balance, however, remained essentially unchanged and exhibited only an adjustment of excretion to the reduced intake. Electrolyte excretion during acute respiratory acidosis in man has also been studied by Elkinson, Singer, Barker and Clark (1132) 1953. In normal subjects exposure to inhalation of 7.5 percent carbon dioxide was imposed for approximately 30 minutes. At the end of this inhalation the average change in electrolyte excretion rate over the individual mean control values in  $uEq./min.$  were as follows:  $HCO_3^- - 63$ ,  $PO_4^- + 10$ ,  $K^+ - 71$ ,  $NH_4^+ + 8$ ,  $Na^+$  and  $Cl^- + 5$ .

In experiments of Epstein, Branscome and Levitin (1133) 1957, rats were exposed to 7.5 percent or 12 percent carbon dioxide in air for one to four days and sacrificed at the end of the experiment. Renal losses of  $Cl^-$  and  $K^+$  increased on the first day of hypercapnia to produce a negative balance of these ions at the end of 24 hours, after which no further net loss occurred. Ammonia excretion was increased on exposure



to carbon dioxide and returned promptly to normal when the rats were given room air to breathe. The data of these authors suggest renal compensation characterized by excretion of  $\text{Cl}^-$  in association with  $\text{K}^+$  and  $\text{NH}_4^+$ , plays an important role in adjustments to chronic respiratory acidosis in the rat. The renal response to acute respiratory acidosis has already been reported by Dorman, Sullivan and Pitts (1131) 1954. In normal dogs receiving infusions of sodium bicarbonate, acute respiratory acidosis induced by breathing 12 percent carbon dioxide results in a significant increase in the rate of reabsorption of bicarbonate bound base, whether expressed in absolute or relative terms. In acute respiratory acidosis, a change in  $\text{P}_{\text{CO}_2}$  of the body fluids is the effective stimulus in enhancing the reabsorption of bicarbonate bound base. A change in pH does not *per se* affect this reabsorptive mechanism. The hypothesis proposed to account for these observations postulated a mechanism involving exchange of hydrogen ions for basic ions, operating throughout the renal tubule. This mechanism, enzymatically facilitated by carbonic anhydrase, is depressed by carbonic anhydrase inhibitors.

The effects of exposure to carbon dioxide in air and oxygen on carbonic anhydrase activity in blood and kidney have been reported by Killion and Schaefer (1136) 1954. In these studies guinea pigs were exposed to 30 percent carbon dioxide in air, and in oxygen for one hour. Carbonic anhydrase activity in blood and kidney homogenates were determined. Carbonic anhydrase activity of the kidney homogenates showed no change after ten minutes of exposure to 30 percent carbon dioxide in air, but increased significantly after 60 minutes of exposure to 30 percent carbon dioxide in air, and was found to return to control levels after two days of recovery. Schaefer (1145) 1955, studying guinea pigs exposed to various carbon dioxide concentrations found that the effect on carbonic anhydrase activity of the kidneys exhibited individual variations. According to Schwartz, Falbriard and Lemieux (1146) 1959, the rate limiting process in bicarbonate reabsorption during acute respiratory acidosis is an enzymatic reaction involving carbonic anhydrase.

1125. Baratz, R. A., A. N. Welter and L. H. Hamilton. Ventilatory, hemodynamic and renal response to I-V infusions of  $\text{CO}_2$ , with observations on the effects of a  $\text{CO}_2$  buffer. *Fed. Proc.*, 1961, 20: 423.

1126. Barbour, A., G. M. Bull, B. M. Evans, N. C. H. Jones and J. Logothetopoulos. The effect of breathing 5 to 7% carbon dioxide on urine flow and mineral excretion. *Clin. Sci.*, 1953, 12: 1-13.

1127. Brazeau, P. and A. Gilman. Effect of plasma  $\text{CO}_2$  tension on renal tubular reabsorption of bicarbonate. *Amer. J. Physiol.*, 1953, 175: 33-38.

1128. Brazeau, P. and A. Gilman. Effects of  $\text{CO}_2$  tension on renal tubular bicarbonate reabsorption. *Fed. Proc.*, 1953, 12: 19.

1129. Carter, N. W., D. W. Seldin and H. C. Teng. Tissue and renal response to chronic respiratory acidosis. *J. clin. Invest.*, 1959, 38: 939-960.

1130. Currie, J. C. M. and E. Ullmann. Polyuria during experimental modifications of breathing. *J. Physiol.*, 1961, 155: 438-455.

1131. Dorman, P. J., W. J. Sullivan and R. F. Pitts. The renal response to acute respiratory acidosis. *J. clin. Invest.*, 1954, 33: 82-90.

1132. Elkinton, J. R., R. B. Singer, E. S. Barker and J. K. Clark. Effects of acute respiratory acidosis on electrolyte excretion in man. *Fed. Proc.*, 1953, 12: 38.

1133. Epstein, F. H., W. Branscome and H. Levitin. The mechanism of hypochloremia in chronic respiratory acidosis. *Clin. Res.*, 1957, 5: 17.

1134. Kaim, J. T., G. Carrasquer, R. Shapiro and W. A. Brodsky. Diffusion of  $\text{CO}_2$  across the renal tubule. *Fed. Proc.*, 1957, 16: 69.

1135. Kennedy, T. J. The effect of carbon dioxide on the kidney. *Anesthesiology*, 1960, 21: 704-716.

1136. Killion, P. J. and K. E. Schaefer. Effects of exposure to 30%  $\text{CO}_2$  in air and in  $\text{O}_2$  on carbonic anhydrase activity in blood and kidney. *Fed. Proc.*, 1954, 13: 78.

1137. Kloos, K. and K. J. Müller. Karyometrische und zytologische Nierenbefunde bei akuter und subakuter experimentellen Hyperkapnie. *Zbl. allg. Path. path. Anat.*, 1960, 100: 464-472.

1138. Kozlov, N. B. The effect of carbon dioxide gas on the content of ammonia, glutamine, and urea in the blood of animals after injection of solutions of ammonium chloride. *Bull. exp. Biol. Med.*, 1961, 50: 1048-1052.

1139. Longson, D. and J. N. Mills. Excess carbon dioxide and morning urine. *J. Physiol.*, 1952, 118: 6P.

1140. Nichols, G., Jr. and K. E. Schaefer. Exchange of electrolytes under carbon dioxide. pp. 145-146 in: *Man's dependence on the earthly atmosphere*. Edited by K. E. Schaefer. The MacMillan Company, New York, 1962, 416 pp.

1141. Nichols, G., Jr., K. E. Schaefer and C. R. Carey. The effect of prolonged exposure to low concentrations of carbon dioxide on acid base balance and electrolytes in blood and urine. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. Rept. no. 292. *Project NM 24 01 20, Rept. no. 1 on Subtask no. 1*, 2 December 1957, 10 pp.

1142. Rector, F. C., Jr., D. W. Seldin, A. D. Roberts, Jr. and J. S. Smith. The role of plasma CO<sub>2</sub> tension and carbonic anhydrase activity in the renal reabsorption of bicarbonate. *J. clin. Invest.*, 1960, 39: 1706-1721.

1143. Relman, A. S., B. Etsten and W. B. Schwartz. The regulation of renal bicarbonate reabsorption by plasma carbon dioxide tension. *J. clin. Invest.*, 1953, 32: 972-978.

1144. Schaefer, K. E. Respiration and acid base balance during exposure to 1.5 per cent carbon dioxide for nine days. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 002 015.03, Rept. no. 9*, 1952.

1145. Schaefer, K. E. Stress of CO<sub>2</sub> and activation of kidney carbonic anhydrase. *Fed. Proc.*, 1955, 14: 131.

1146. Schwartz, W. B., A. Falbriard and G. Lemieux. The kinetics of bicarbonate reabsorption during acute respiratory acidosis. *J. clin. Invest.*, 1959, 38: 939-944.

1147. Schwartz, W. B., G. Lemieux and A. Falbriard. Renal absorption of bicarbonate during acute respiratory alkalosis. *J. clin. Invest.*, 1959, 38: 2197-2201.

1148. Scribner, B. H., G. M. Bogardus, K. Fremont-Smith and J. M. Burnell. Potassium intoxication during and immediately following respiratory acidosis. *J. clin. Invest.*, 1954, 33: 965.

1149. Scribner, B. H. and J. M. Burnell. The effect of respiratory alterations of pH on the internal equilibrium of potassium. *J. clin. Invest.*, 1955, 34: 919.

1150. Valtin, H. and S. M. Tenney. Carbon dioxide diuresis at high altitude. *Fed. Proc.*, 1960, 19: 362.

1151. Valtin, H., I. D. Wilson and S. M. Tenney. CO<sub>2</sub> diuresis, with special reference to role of the left atrial stretch receptor mechanism. *J. appl. Physiol.*, 1959, 14: 844-848.

### K. SPLEEN

Studies of Ramlo and Brown (1152) 1959, indicate that splenic contraction produced in dogs by breathing 30 percent carbon dioxide is mediated by both splenic nerves and by the adrenal glands. Nerve stimulation appears to act more rapidly, but contraction still occurs in the absence of all innervation. Neither bilateral adrenalectomy nor splenic denervation alone completely blocked the splenic response. In order to block the splenic response completely, both denervation of the spleen and bilateral adrenalectomy were necessary.

1152. Ramlo, J. H. and E. B. Brown, Jr. Mechanisms of splenic contraction produced by severe hypercapnia. *Amer. J. Physiol.*, 1959, 197: 1079-1082.

### L. TOLERANCE

According to Chapin (1153) 1955, survival times of mice exposed to high carbon dioxide

varied with different oxygen concentrations. Longer survival times were encountered when the carbon dioxide concentration was lowest, and with exposures to 40 percent carbon dioxide when oxygen concentrations were between 12 and 20 percent. Oxygen under high pressure failed to produce convulsions in the presence of high carbon dioxide concentrations.

1153. Chapin, J. L. Survival of mice in high CO<sub>2</sub> environments at varying O<sub>2</sub> tensions. pp. 255-258 in: *Studies in respiratory physiology. Second series. Chemistry, mechanics, and circulation of the lung*. Edited by H. Rahn and W. O. Fenn. Wright Air Development Center, Dayton, Ohio. Aero medical laboratory. *WADC Tech. Rept. 55-537*, November 1955, 438 pp.

### M. ACCLIMATIZATION

For studies of acclimatization to carbon dioxide and respiratory responses to carbon dioxide during altitude acclimatization, the following bibliographic papers should be consulted: Kellogg, Reed and Todd (1158) 1958; Kellogg (1157) 1961; and Kellogg (1156) 1960.

The effects of chronic hypercapnia on electrolyte and acid-base equilibrium have been reported by Polak, Haynie, Hays and Schwartz (1159) 1961. These studies were carried out in dogs exposed to atmospheres of 11 to 13 percent carbon dioxide for periods of 6 to 15 days. A consistent pattern of response was found, characterized by a sharp rise in plasma bicarbonate concentration during the first day of exposure and a subsequent slower rise over the next 5 or 6 days, to a final concentration ranging from 35-38 mEq./L.

Schaefer, Nichols and Carey (1162) 1960, have reported that human subjects exposed to 3 percent carbon dioxide in 21 percent oxygen for prolonged periods, showed a characteristic respiratory adaptation, which consisted among other factors in a reduction of the normal ventilatory response to increased concentration of carbon dioxide. In further subjects exposed to 1.5 percent carbon dioxide in 21 percent oxygen for 42 days, the respiratory minute volume and alveolar carbon dioxide tensions were found to be increased throughout the exposure. No significant changes were observed in vital capacity, inspiratory and expiratory reserve, or tidal volume. A slight respiratory acidosis was present during the first 23 days of exposure, as indicated in the



lowering of pH, which was associated with a decreased carbon dioxide excretion in the expired air and urine. A phase of compensated respiratory acidosis followed, during which the pH, as well as the carbon dioxide excretion, returned to the initial level. After transition to air the carbon dioxide excretion in expired air and urine reached a peak and returned to normal values within a week. At the end of the exposure to 1.5 percent carbon dioxide, a significant depression of the ventilatory response to 5 percent carbon dioxide was found, similar to the results under 3 percent carbon dioxide. Similar studies were reported by Schaefer, Hastings, Carey and Nichols (1161) 1963.

1154. Balke, B. The effect of altitude acclimatization on CO<sub>2</sub> tolerance. *Fed. Proc.*, 1959, 18: 7.

1155. Chapin, J. L. Evidence for simultaneous lowering of upper and lower limits of CO<sub>2</sub> tolerance. *Fed. Proc.*, 1956, 15: 34.

1156. Kellogg, R. H. Acclimatization to carbon dioxide. *Anesthesiology*, 1960, 21: 634-641.

1157. Kellogg, R. H. The role of CO<sub>2</sub> in altitude acclimatization. pp. 379-395 in: *The regulation of human respiration*. Edited by D. J. C. Cunningham and B. B. Lloyd. F. A. Davis Co., Philadelphia, 1961, 591 pp.

1158. Kellogg, R. H., D. J. Reed and A. R. Todd. Comparison of acid-base balance and respiratory response to CO<sub>2</sub> during altitude acclimatization. *Fed. Proc.*, 1958, 17: 84.

1159. Polak, A., D. G. Haynie, R. M. Hays and W. B. Schwartz. Effects of chronic hypercapnia on electrolyte and acid-base equilibrium. I. Adaptation. *J. clin. Invest.*, 1961, 40: 1223-1237.

1160. Schaefer, K. E. A concept of triple tolerance limits based on chronic carbon dioxide toxicity studies. *Aerospace Med.*, 1961, 32: 197-204.

1161. Schaefer, K. E., B. J. Hastings, C. R. Carey and G. Nichols, Jr. Respiratory acclimatization to carbon dioxide. *J. appl. Physiol.*, 1963, 18: 1071-1078.

1162. Schaefer, K. E., G. Nichols and C. R. Carey. Respiratory adaptation to chronic CO<sub>2</sub> exposure. *Fed. Proc.*, 1960, 19: 381.

1163. White, C. S., J. H. Humm, E. D. Armstrong and N. P. V. Lundgren. Human tolerance to acute exposure to six percent carbon dioxide in air and in oxygen. USAF, Randolph Field, Texas. School of aviation medicine. Project 21-1402-0001, Rept. no. 1, March 1953, 13 pp.

## N. PATHOLOGICAL CHANGES

Studies of pathological changes resulting from experimental exposure to high concentrations of carbon dioxide, published before 1951, draw attention to irreversible changes, including damage of the alveolar walls of the lungs and cell necrosis

with dead cells and debris in the liver, kidney and brain. High degrees of hyperemia of the lung have been found, as well as pulmonary edema in some cases. In some cases the alveoli of the lungs were dilated, as in emphysema, with dense infiltration of leukocytes in extensive areas. Hyperemia has also been found extensively throughout the liver. In some liver cells the nuclei were pycnotic. Some cases revealed hyperemia and necrosis of the kidneys. In some animals there were irreversible changes in the central neurons. The liver and kidneys appeared to be the first organs to be impaired. The straight uriniferous tubules showed vacuolar degeneration and necrosis. With high carbon dioxide concentrations there were also fat deposits in the renal pyramids and the glomeruli were swollen. Regarding nervous system damage, those neurons most sensitive to hypoxia, such as those in the cerebral cortex, were found to be protected from severe histopathological changes. Following exposure to carbon dioxide, the cells of the more primitive levels of the brain, less sensitive to oxygen lack, sustained the greatest structural damage as a result of high carbon dioxide inhalation. In acute exposures to carbon dioxide the cell changes were generally reversible but irreversible changes were observed in some large motor cells. In acute experiments neurons showed slight swelling with chromatolytic changes, more marked in the periphery of the cells. The nuclei were swollen, as were also the nucleoli and there was also vacuolation. In chronic experiments there was severe swelling of the cells with chromatolysis. Vacuolar degeneration of cells of the hypophysis was also reported. More recently, Kaplan, Williams, Carpenter, Annegers and Lee (1164) 1956, have carried out studies on monkeys to examine the possible toxic effects of high carbon dioxide concentrations. They exposed animals to 3 and 4.5 percent carbon dioxide for periods up to 112 days. The oxygen concentration was maintained at 21 percent. In the 3 percent carbon dioxide experiment, 10 animals were exposed to carbon dioxide while 10 others were kept at ordinary atmospheric conditions and served as controls. In the 4 percent carbon dioxide experiment, 10 animals were kept at ordinary atmospheric conditions for three weeks to obtain control meas-

urements prior to the exposure. The following constituents of the blood or plasma were measured: carbon dioxide content, pH,  $P_{CO_2}$ , NPN, calcium, phosphorus, glucose, sodium, potassium, chloride, bilirubin, cephalin flocculation, oxygen content, hemoglobin, hematocrit, sedimentation rate, white blood cell and eosinophil counts. Autopsies were performed on the animals during or at the end of the exposure period. During exposure to 3 percent carbon dioxide, the animals maintained their weights and showed no significant alterations in the constituents of their blood. However, during exposure to 4.5 percent carbon dioxide they developed anorexia, dyspnea, cough, dehydration and loss of weight. The only changes observed recorded in the constituents of the plasma were elevation of the carbon dioxide content and  $P_{CO_2}$  and reduction of the hydrogen ion concentration. Morphologic findings in the group exposed to 4.5 percent carbon dioxide included: 1) a diffuse pneumonitis, and 2) hepatic edema, manifested by intracellular watery vacuoles and perisinusoidal edema. The lungs showed some features in common with the so-called uremic pneumonitis. The most severe changes were seen in animals with the most severe respiratory acidosis. A possibility that the pathological findings might have been due to pulmonary infestation was not ruled out.

1164. Kaplan, S. A., S. N. Stein, R. B. Williams, H. M. Carpenter, J. Annegers and R. E. Lee. Effects of prolonged exposure of monkeys to carbon dioxide. *Fed. Proc.*, 1956, 15: 105.

1165. Millikan, C. H. Evaluation of carbon dioxide inhalation for acute focal cerebral infarction. *Arch. Neurol. Psychiat.*, 1955, 73: 324-328.

1166. Schaefer, K. E., M. Avery and K. Bensch. Effect of  $CO_2$  intoxication on the surface characteristics of lungs and morphology of alveolar epithelial cells. *Fed. Proc.*, 1963, 22: 339.

## V. INERT GASES

### A. GENERAL STUDIES

For papers dealing generally with the effects of the inert gases, the reader should consult the references listed in the following section.

1167. Carpenter, F. G. Depressant action of inert gases on the central nervous system in mice. *Amer. J. Physiol.*, 1953, 172: 471-474.

1168. Carpenter, F. G. Anesthetic action of inert and unreactive gases on intact animals and isolated tissues. *Amer. J. Physiol.*, 1954, 178: 505-509.

1169. Carpenter, F. G. Inert gas narcosis. pp. 124-130 in: *Proceedings of the underwater physiology symposium*. Edited by L. G. Goff. National Research Council, Washington, D. C. N.R.C. Publication 377, 1955, 153 pp.

1170. Carpenter, F. G. Alteration in mammalian nerve metabolism by soluble and gaseous anesthetics. *Amer. J. Physiol.*, 1956, 187: 573-578.

1171. Carpenter, F. G. Kinetics of blockade in peripheral nerve fibers produced by anesthetic gases. *Fed. Proc.*, 1959, 18: 23.

1172. Cook, G. A. Argon, helium and the rare gases. *The elements of the helium group. Volume I*. Interscience Publishers, New York, 1961, 392 pp.

1173. Cook, G. A. Argon, helium and the rare gases. *The elements of the helium group. Volume II*. Interscience Publishers, New York, 1961, 818 pp.

1174. Cook, S. F. The effect of helium and argon on metabolism and metamorphosis. *J. cell. comp. Physiol.*, 1950, 36: 115-127.

1175. Cook, S. F. and H. A. Leon. Physiological effects of inert gases. USAF. Holloman Air Force Base, Mexico. Missile development center. *Tech. Rept. AFMDC-TR-59-26*, June, 1959, 35 pp.

1176. Davis, H. S., W. F. Collins, C. T. Randt and W. H. Dillon. Effect of anesthetic agents on evoked central nervous system responses: gaseous agents. *Anesthesiology*, 1957, 18: 634-642.

1177. Ebert, M., S. Hornsey and A. Howard. Effect of inert gases on oxygen-dependent radiosensitivity. *Nature, Lond.*, 1958, 181: 613-616.

1178. Featherstone, R. M. and C. A. Muehlbaeher. The current role of inert gases in the search for anesthesia mechanisms. *Pharmacol. Rev.*, 1963, 15: 97.

1179. Frankel, J. and H. A. Schneiderman. The effects of nitrogen, helium, argon and sulfur hexafluoride on the development of insects. *J. cell. comp. Physiol.*, 1958, 52: 431-451.

1180. Johnson, W. J. and J. H. Quastel. Narcotics and biological acetylations. *Nature, Lond.*, 1953, 171: 602-605.

1181. Lanphier, E. H. Nitrogen-oxygen mixture physiology. Phases I and II. U.S. Navy, EDU, Naval Gun Factory, Washington, D.C. *Rept. 7-55, Proj. NS185-005, Subtask 5*, 30 June 1955, 35 pp.

1182. Lord, G. P., G. F. Bond and K. E. Schaefer. Pulmonary function in man breathing a helium-oxygen-nitrogen atmosphere at 7 atmospheres absolute pressure for 12 days. *Fed. Proc.*, 1964, 23: 117.

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## B. NITROGEN

Nitrogen narcosis (1222), characterized by symptoms similar to alcohol intoxication, becomes evident first at a depth of about 100 feet and causes ineffectiveness in most divers at 200 feet. Like alcohol the effects of nitrogen vary with the individual person and its hazards can be minimized within limits by conscious effort. Similar to other inert gases, which are soluble in oil or fat, its anesthetic potency increases under pressure. Argon, krypton and xenon have even greater narcotic effects than nitrogen. The general subject of nitrogen narcosis has been treated by Miles (1217) 1962. At levels of 100 to 150 feet depth there is light-headedness, increased self-confidence and loss of fine discrimination. At 150 to 200 feet subjects become jovial and garrulous, and there is some dizziness. At 200 to 250 feet there is laughter and possibly hysteria, with lessened powers of concentration and some peripheral numbness and tingling with delayed stimulus response. At 300 feet there is depression and impaired neuromuscular coordination. At 350 feet consciousness may be lost and there is increased danger of oxygen toxicity. All of these symptoms are seen with air under pressure. It appears that resistance to nitrogen narcosis is improved with diving experience but the adaptation is not permanent. In order to maintain the adaptation, dives once a week to 300 feet seem to be required. Only a few

minutes at depth is needed. As Burnett (1206) 1955, has stated, the exact cause of nitrogen narcosis has as yet not been definitely established, although means of combating the effect of compressed air on human subjects at great depths are available by the use of helium in substitution for nitrogen. For a discussion of the theories of inert gas narcosis, a paper by Miller (1218) 1963, may be consulted. Rahn (1219) 1961, has discussed the role of nitrogen gas, in general, in various biological processes.

According to Rashbass (1220) 1955, and Lanphier and Busby (1215) 1962, carbon dioxide retention can be ruled out as a primary cause of nitrogen narcosis. That nitrogen narcosis does not depend on an increase of arterial  $P_{CO_2}$  has also been reported by Lanphier (1214) 1963. In a review of the physiological effects of high pressures with nitrogen and oxygen, Fenn (1208) 1961, states that nitrogen under high pressure and argon under high pressure, but not helium, act like other anesthetics in favoring water-in-oil rather than oil-in-water emulsions of dilute NaOH solutions in olive oil. The effect is small but appears to be real. This suggests that inert gases may make the lipoidal surface layer of cells relatively more continuous and therefore less permeable.

To test the hypothesis that nitrogen narcosis is really carbon dioxide narcosis, Taylor (1221) 1962, caused human subjects to hyperventilate in order to reduce carbon dioxide under conditions of supposed nitrogen narcosis. The narcotic effect was determined by comparison of the number of correct answers during two minutes of arithmetic at 250 feet with the number correct answers under control conditions. At a simulated depth of 250 feet there was a marked reduction in the correct number of sums and a small but significant rise in carbon dioxide concentration. Five minutes of normal breathing abolished increased alveolar carbon dioxide and there was a reduction in alveolar carbon dioxide concentration with no further alleviation of the narcosis. Therefore, with the possible exception of the first few minutes, carbon dioxide was considered by the author not to contribute to the causation of the narcosis.

Lambertsen (1213) 1961, has pointed out that inert gases differ in the partial pressures required

to produce a narcotic effect. For full unconsciousness and analgesia from nitrogen, 38 atmospheres or 1200 feet depth is required, but euphoria occurs between 3.5 and 5 atmospheres (80–120 feet depth), and a state of severe "alcoholic" intoxication is obtained at 250 feet. No narcotic effect of helium has been found yet (up to 1000 feet). The narcotic effect increases with molecular weight and with the solubility of the gas in lipids. It is noteworthy that the British experience in recent diving trials demonstrates some narcosis from helium at 750 to 800 feet depth.

In an important paper on the neuropharmacologic and neurophysiologic changes in inert gas narcosis, Bennett (1199) 1963, has reported the response of rats to electroshock as a measure of the extent of inert gas narcosis (argon and nitrogen at 180 lbs. per sq. in.) before and after Frenquel administration. The experiments demonstrate that argon is more narcotic than nitrogen and nitrogen in turn is more narcotic than helium. The administration of Frenquel protected against inert gas narcosis. The increase in ventilation at 180 psi in air was 50.2 percent,  $\pm 4$  percent, whereas with Frenquel it was 1.21 percent,  $\pm 2.45$  percent (not significantly different from atmospheric pressure). The dosage of Frenquel was 40 mg. When three men were compressed to 10 ATA Frenquel in doses of 10, 300 and 900 mg. had no protective effect against narcosis, as measured by arithmetic and manual dexterity tests. At 300 feet depth on air there was a significant rise in the critical fusion frequency, but when 3600 mg. of Frenquel was given no increase was seen, but there were some drug side effects. Synaptic potentials evoked by sciatic nerve stimulation were depressed by increased inert gas pressures. When argon (220 psi) with 15 psi oxygen were used, there was an initial depression of potential followed by a period of augmentation and then a progressive depression and sometimes blockade. With nitrogen the effect was less; with helium there was no effect. In experiments reported by Bennett and Glass (1204) 1957, cortical electrodes were inserted into the skull of rabbits with the tips of the electrodes just resting on the dura. Recordings were taken at sea level and at various simulated depths to a maximum of 250 feet, and at

different stages of decompression. The animals appeared more restless at depth than at the surface and the EEG confirmed these findings. After decompression the slower activity (5–6 cycles per second from the cortex) returned. When a 20–25 percent nitrous oxide mixture was given (isonarcotic with air at 250 feet depth) the EEG was slower and resembled sleep. In human studies divers were the subjects of EEG recording. Control EEG records with the subjects eyes closed revealed a 9–11 cycle pattern of 20–30  $\mu$ V. This was blocked by opening the eyes (alpha blocking). Mental tasks were also administered, and it was found that the blocking of the alpha rhythm by mental problems was abolished after varying times at pressure. At higher pressures this time was short and at lower pressures it was longer. This relationship between time and abolition of blocking at depth suggested to the authors a diffusion process. It was found that a high partial pressure of nitrogen was primarily responsible for this effect. A suggested site of action of nitrogen is the reticular activating system in the brain stem. It was concluded that isonarcotic concentration of nitrous oxide studies suggest that the tables by Carpenter are not strictly applicable to human subjects. In the latter there is a tendency to a higher degree of narcosis than would be found at an equivalent depth of compressed air. Related studies are reported by Bennett and Glass (1205) 1961, and Bennett (1196) 1958. In a study of the fusion frequency of flicker and nitrogen saturation, Bennett (1200) 1959, carried out experiments to measure the flicker fusion frequency of men exposed to raised pressure of compressed air. In five subjects tested, four showed and maintained a slight fall and the other a rise in fusion frequency while at pressure. Each subject was tested at seven different pressures. The time required for this change in perception of fusion frequency or the nitrogen threshold was found to be inversely proportional to the square of the pressure.

Ch'un (1207) 1959, found that the reflex activity of the spinal cord was lowered in decerebrate cats at a pressure of 9 atmospheres of nitrogen partial pressure.

In experimental studies of prevention of narcosis by inert gases at high pressures, Bennett



(1198) 1963, developed a technique for quantitative evaluation of inert gas narcosis in rats. The response of 46 adult Wistar rats to minimal electroshock was used in 102 experiments to determine the narcotic effect of nitrogen at 12.6 and 13.5 ATA and argon at 12.6 ATA, before and after the oral, intraperitoneal or intravenous administration of Frenquel. This drug controlled the narcotic effect produced by these inert gases at pressure without, so far as could be observed, the supervention of undesirable side effects. The effective dose was 40 mg. (130–150 mg./Kg. body weight). Lower doses were only partially effective, and the maximum protective action of the drug was observed about 48 hours after its administration. Similar studies are reported by Bennett, Dossett and Kidd (1202) 1959. These same authors (1203) 1960, found in rats that the least narcotic effect was produced by mixtures of 65 psi of oxygen and 130 psi of nitrogen. In a comparison of the effects of drugs on nitrogen narcosis and oxygen toxicity in rats, Bennett (1197) 1962, found that Frenquel, phenacetin, Carbachol, Doriden and aspirin all protected against nitrogen narcosis and also delayed the onset of oxygen convulsions. There was variation among the drugs in the protection afforded; Carbachol was most effective. Some drugs, such as methedrine, enhanced the sensitivity of rats to narcotic effects of nitrogen and oxygen convulsions. Adrenalin, Scopolamine and Physostigmine had little effect. The author concluded that both nitrogen and oxygen involved impairment of at least some similar mechanisms and that drugs which control or enhance impairment produced by one gas will act similarly with the other.

Psychomotor testing indicates a detriment in performance of subjects during air dives to five atmospheres. Hesser (1210) 1963, in a study of factors responsible for compressed air narcosis, examined human performance alterations induced through exposure to different nitrogen-oxygen partial pressures at increased ambient pressure. In these studies 12 subjects were subjected to psychomotor tasks in a dry chamber. A rise in air pressure from 1–5 atmospheres resulted in a slight tendency towards impaired performance if oxygen was added (39.8 percent oxygen in nitrogen). At 6.6 atmospheres the impairment in performance was increased. From

this experiment the author concluded that the narcosis is not due to interference with the oxidative processes in the tissues. In a further study of performance impairment as a function of nitrogen narcosis, Kiessling and Maag (1211) 1960, and (1212) 1962, carried out some studies in which Navy divers individually performed air dives in a high pressure chamber for 40 minutes at a simulated depth of 100 feet. Each experimental session consisted of three phases: (1) a measure of performance on choice reaction time, motor coordination, and conceptual reasoning at sea level in the chamber; (2) three 12 minute periods at a pressure equivalent to 100 feet of sea water, during which equal time was allocated to each of the three tests; and (3) a final measure during the decompression stop at 10 feet. Statistically significant decreases in performance for all subjects on all tests were found with the greatest decrement occurring on the reasoning test, the least on motor coordination. Decreased performance occurred as the pressure increased and remained relatively constant with duration of exposure.

In a study of the role of nitrogen in breath-holding at increased pressures, Hesser (1209) 1962, conducted studies to test the hypothesis that the increased ability to hold the breath at increased ambient pressure is due to increased nitrogen pressure in addition to the concomitant increase in oxygen tension. In Hesser's studies eight experienced subjects were exposed to air, 100 percent oxygen, or 5 percent oxygen in nitrogen, in a dry recompression chamber at pressures from 1–4 ATA for 15 minutes before breath-holding. The average expiratory reserve volume at the breaking point ranged from 1.02 to 1.34 liters. With air the maximum breath-holding time (2.8 times longer at four than at one atmosphere) and the breaking point of  $P_{CO_2}$  increased with increasing pressure. The breaking points after 5 percent oxygen in nitrogen at three and four atmospheres were located on the same curve as air breathing or reduced pressure, suggesting no effect of nitrogen on breath-holding ability. Breath-holding time with air at four atmospheres was significantly longer and the  $P_{CO_2}$  significantly higher than oxygen breathing at one atmosphere, despite a higher  $P_{CO_2}$  in the latter. After testing the theory that 15

minutes was not long enough for the chemosensitive control mechanisms to come into equilibrium with a new oxygen tension, the original hypothesis was still disproved within the pressure range studied. It was also demonstrated at ambient pressure that an oxygen threshold exists of 350 mm. Hg above which the breaking point is entirely  $P_{CO_2}$  dependent. The  $P_{CO_2}$  threshold was 60 mm. Hg. No symptoms of oxygen toxicity were noted in five hours of 100 percent oxygen breathing at pressures from 0.3 to 2.5 atmospheres.

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### C. XENON

The anesthetic properties of xenon have been studied in both animals and human subjects by Cullen and Gross (1223) 1951. Human subjects inhaled either 50-50 mixtures of xenon and oxygen or 50-50 mixtures of nitrous oxide and oxygen from a closed system spirometer with soda lime in the circuit. Oxygen was added according to the metabolic requirements of the individual. Pain threshold measurements indicated a uniform 15 percent increase in pain threshold with either gas mixture. Each subject reported more pronounced subjective symptoms of narcosis with the xenon mixture than with nitrous oxide. Two human subjects who inhaled a mixture containing 70 percent xenon and 30 percent oxygen for three minutes experienced pronounced narcotic effects with partial loss of consciousness. It appeared that xenon had anesthetic properties approximately equivalent to ethylene.

The basis of the anesthetic action of xenon is not understood. Comparative *in vitro* studies of guinea pig brain oxidations, as influenced by xenon and nitrous oxide and conducted by Pittinger, Featherstone, Cullen and Gross (1228) 1951, have shown that xenon and nitrous oxide in 80-20 mixtures with oxygen did not suppress *in vitro* oxygen uptake of guinea pig brain tissue, either before or after addition of glucose as a substrate. The addition of the substrate did result in significant increases in oxygen consumption but no significant difference existed among 80-20 xenon-oxygen, nitrous oxide-oxygen, or nitrogen-oxygen mixtures in this respect.

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### D. KRYPTON

Krypton is referred to here because it is an inert gas which can be readily used for saturation and desaturation studies of animals or men at sea level or under pressure. The gas is particularly convenient because it can be readily tagged and has a short half life. Krypton is thus a potentially important research tool in that it can be used to follow the distribution of inert gases throughout the body. No evidence has been found in the literature of any physiological effect of krypton at sea level pressures. The radioactive isotope krypton 85 has been used to measure blood flow (Brun, Crone, Davidsen, Fabricius, Hansen, Lassen and Munck (1230), 1955) coronary blood flow (Hansen, Haxholdt, Husfeldt, Lassen, Munck, Sørensen and Winkler (1231), 1956) and cerebral blood flow (Lassen and Munck (1232), 1955).

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### E. HELIUM

The use of helium-oxygen mixtures has not only increased the depths to which divers can descend, but it has also greatly enhanced their performance at these depths. By the use of helium-oxygen mixtures the respiratory effort is greatly diminished. The practical uses of helium-oxygen mixtures in diving are discussed in a later section.

The use of helium-oxygen mixtures in alleviating symptoms in patients with bronchial asthma has been examined by Schiller, Lowell, Lynch and Franklin (1249) 1955. In severely ill patients no significant change was observed in expiratory reserve volume, inspiratory capacity, vital capacity or in speed of flow during performance of the vital capacity testing. On the other hand in the same measurements using less seriously ill patients slightly larger values were obtained with helium, thus the use of helium has definite therapeutic limitations.

The use of helium-oxygen mixtures, because of lower density, causes a characteristic high-pitched "Donald Duck" voice production with important effects on speech intelligibility. Several studies have been undertaken to examine this problem. Sergeant (1252) 1963, carried out a study to see if the "Donald Duck" voice effect

would remain on prolonged exposure to helium-oxygen mixtures or whether adaptation would occur. In general, the effects tend to persist. However, Sergeant reported in sea level studies that intelligibility showed deterioration after two days of exposure to helium-oxygen mixtures, but by the fourth to sixth day's exposure a return to more normal speech was found. For further studies on speech quality and frequency during respiration of helium-oxygen mixtures, papers by Sergeant (1251) 1963, Dublin, Baldes and Williams (1245) 1940, and Beil (1240) 1962, should be consulted. Research is needed on the development of electronic speech unscramblers to convert this "Donald Duck" type of voice into more intelligible speech.

Cook and South (1242) 1953, have shown that helium increases the rate of oxygen consumption of mouse brain slices *in vitro*. The same authors (1253) 1953, found that the use of helium relative to nitrogen under anaerobic conditions causes a depression of the glycolytic rates in both mouse liver slices and diaphragm. There is also an increase in the carbon dioxide evolution and lactic acid production of mouse liver homogenates oxidizing either glucose and hexose diphosphate, or hexose diphosphate alone. It is hypothesized that helium does not alter the substrate utilized by the tissue. Also it is believed that the gas interferes in some way with the cyanide-cytochrome oxidase bond, but may not affect cytochrome oxidase in the absence of cyanide. The citric acid cycle is not subject to the influence of helium in tissue slices but is altered in an unexplained fashion in homogenates. It is postulated that a rearrangement of particular surfaces may be the significant factor here. The glycolytic process is the site of both an inhibitory and an acceleratory effect of helium. The locus of the inhibition lies above the aldolase reaction and that of the acceleration between the aldolase and enolase reactions.

Cross (1244) 1953, has reported the effect of increased atmospheric pressures and inhalation of 95 percent oxygen and helium-oxygen mixtures on the viability of the bowel wall and the absorption of gas in closed loop obstructions in dogs. Comparisons were made in groups of dogs breathing air at pressures of 1 to 4 atmospheres for 6 to 24 hours; breathing 95 percent



oxygen at pressures of 1 to 2.5 atmospheres for periods of 6 to 12 hours; breathing helium-oxygen mixtures at 1 to 2 atmospheres for periods of 6 to 24 hours with observations on the effect of increased atmospheric pressure on the maintenance of viability of the bowel in closed loop obstructions. It was found that the absorption rate of injected air from closed loops was increased under conditions of increased atmospheric pressure no matter what gas had been inhaled, the magnitude of the increase being directly proportional to the increase in atmospheric pressure. Ninety-five percent oxygen inhalation caused the best absorption rates of gas from the closed loops whether breathed at 1 atmosphere or under conditions of increased pressure. The limiting factor in the use of oxygen was the onset of oxygen intoxication. The dogs tolerated 95 percent oxygen at 2 atmospheres for 6 hours, or for 12 hours at 1 atmosphere, but the incidence of oxygen intoxication was high in those dogs breathing oxygen for 6 hours at  $2\frac{1}{2}$  atmospheres or for 12 hours at 2 atmospheres of pressure. This oxygen intoxication could be avoided when the dogs breathed helium-oxygen mixture, but the absorption rates of the bile gas were up to 17 percent less than with oxygen breathing for any given pressure or time period. The helium diffused into the bowel as the nitrogen diffused out, and the distention was maintained. Not only was there an increased absorption of gas from the bowel under conditions of increased pressure but also the viability of the bowel wall was well maintained. In a study of the mechanism by which helium increases metabolism in small mammals Leon and Cook (1248) 1960, studied the oxygen consumption of male rats determined at three different ambient temperatures in air and the equivalent helium-oxygen mixture. It was found that when the ambient temperature is near the skin temperature of the rat the effect of helium is insignificant. If the ambient temperature is lowered helium induces an increased metabolic rate over air at the same temperature. Since helium has a thermal conductivity about six times greater than nitrogen it was concluded that the accelerated metabolism is in response to greater heat loss in the presence of helium and that the magnitude of this response is proportional to the thermal gradient

between the animal and the environment. Young and Cook (1256) 1953, have reported on the effect of helium on the gas exchange of mice as modified by body size and thyroid activity. Two groups of male mice, one averaging 25 grams in weight and the other 30 grams, were tested in air and in a mixture of 20 percent oxygen in helium. Helium accelerated the oxygen consumption in both groups. The degree of acceleration was greater in the heavier group in which the standard metabolism in air was lower. Similar experiments were performed with normal mice, with mice which had been radiothyroidectomized with  $I^{131}$ , and with mice which had been fed heavy doses of desiccated thyroid gland. The acceleration of oxygen consumption due to helium was greatest in the slowly metabolizing thyroidectomized group (intermediate with the normals and least with the hyperthyroid animals). It was concluded that the effect of helium is inversely proportional to the level of the standard metabolism regardless of the nature of the factors which initially determine that level. An interesting new biological effect of helium has been reported by Schreiner, Gregoire and Lawrie (1250) 1962, in studies which show a close correlation of growth rate with the molecular weight of the inert gas in a gaseous mixture containing oxygen. The mold *neurospora crassa* was grown in gaseous environments of helium, neon, argon, krypton, xenon or nitrogen containing 5 percent oxygen. There was a close correlation of growth rate  $R$  (in millimeters/hour at  $30^{\circ}\text{C}.$ ) with molecular weight  $MW$  ( $MW$  of the chemically inert gas). This relationship is described by the empirical equation:  $R = 3.88 - 0.1785 (MW)^{1/2}$ .

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## VI. HEAT AND HUMIDITY PROBLEMS

### A. PHYSIOLOGICAL EFFECTS OF RAISED TEMPERATURES

There are many compensatory mechanisms which serve to protect the organism from high heat levels and to maintain the constancy of the internal temperature of the body. Under certain conditions of stress, as in violent exercise, elevated temperatures of the body are observed

with no untoward effects. Although rectal temperatures as high as 106-108°F. have been observed in short foot races in athletes without harm, such hyperpyrexia if prolonged for several hours leads to thermal injury of certain body cells, particularly in the central nervous system. Dehydration and circulatory collapse may result from prolonged heat exposure. Compensatory mechanisms leading to increased blood volume and re-direction of circulation through the periphery, as well as loss of body fluid stores, may lead to circulatory shock even before the body temperature begins to rise significantly (heat collapse). In some instances of severe exposure to heat associated with muscular work there may be rapid failure of circulatory adjustments and sweating so that true body hyperthermia results (heat stroke). For a general review of pathological effects of heat on man a review by Carter (1262) 1960, may be consulted. In a study of cardiovascular responses to acute heat stress, Marshall, Koroxenidis and Shepherd (1277) 1961, have examined cardiac output, digital heat flow and forearm blood flow simultaneously in healthy subjects. Initially with subjects cool the cardiac index was 3.00 liters, the heart rate 66, the stroke volume 85 ml. and digital heat flow 30 BTU/M.<sup>2</sup>/hr. (mean values). Indirect heating was then imposed for 45 minutes. The heat flow rapidly increased to a plateau when sweating was first noted 15 minutes after heating began. In contrast, gradual and parallel increases in output and forearm flow occurred throughout the 45 minute period. At the end when the subjects were sweating profusely and the oral temperature was 99.5°F. or more, cardiac index rose to 4.70 liters, the heart rate to 94, the stroke volume to 95 ml. and the heat flow to 240 BTU/M.<sup>2</sup>/hr. Thus increased skin blood flow during heat stress is sufficient to increase cardiac output by more than 50 percent, and this increase in output is achieved mainly by tachycardia. Kanter (1270) 1956, has experimentally investigated glucose regulation in dogs exposed to high environmental temperatures. Exposure of 12 dogs to 120°F. four hours without access to water resulted in an average fall of whole blood glucose of 19 percent and of plasma glucose by 13 percent, in spite of an average final dehydration of 5.6 percent in body weight. One



might expect dehydration to cause an increase in concentration, yet under the experimental conditions imposed hypoglycemia resulted. That the fall in glucose levels was the result of dehydration *per se* therefore seemed unlikely. To test this point, seven experiments were conducted in which dogs were exposed to heat but the water balance was maintained by administration of water through a stomach tube. Here hypoglycemia again was found but the regime of the experiment was not responsible for the hypoglycemia. It appears that the fall in glucose concentration is associated with the increase in deep body temperature, for when dogs were exposed to milder air temperatures (100°F.) dehydration, but only slight elevation in rectal temperature, occurred with no fall in glucose levels. A finding of hyperglycemia in man exposed to desert-like conditions has been reported (in contrast to the hypoglycemia found in dogs), and may possibly be explained by the presence of dehydration but with an absence of elevation of deep body temperature in human studies.

Salt losses of men working in hot environments have been examined by Weiner and van Heyningen (1285) 1952. Loss of chlorides in sweat and urine occurs in human subjects working in hot conditions for short periods. Acclimatization to heat is accompanied by a decrease in chloride concentration of body sweat, only if negative chloride balance is induced by restriction of chloride intake. Sweating for short periods (two hours) in unacclimatized subjects brings about compensatory reduction of urinary chlorides manifested after the subject leaves the hot environment. This reduction is so great that total loss of chloride may be less on days in which sweating occurs. Malhotra, Sharma and Sivaraman (1276) 1959, have presented data on salt requirements in the tropics based on observations on 24 acclimatized Indian subjects given diets containing 16.2, 11.2, 8.7, 6.2 and 3.1 gms. of salt per day. The adequacy of the salt diet was tested by measurements of chloride secretion in the urine, by changes observed in thiocyanate space and plasma chloride concentration at the start and after the subjects had been on the restricted salt diet for a week. Sweat and chloride losses in different environmental temperatures were studied. The salt requirements of subjects walk-

ing for two hours in the sun at a speed of about 2.5 miles per hour was found to be about 6.2 gms. per day when the mean maximum environmental temperature was 100.7°F. (dry bulb). The requirement was found to increase by 0.063 gm. per degree rise in dry bulb temperature for two hours exercise. Kanter has reported a decrease in glomerular filtration rate and renal plasma flow as a result of hyperthermia. This study was carried out on anesthetized dogs using creatinine clearance to measure the glomerular filtration rate and PAH clearance to measure renal plasma flow. The glomerular filtration rate in eight mildly dehydrated dogs fell from a control value of  $67.6 \pm 5.2$  ml. per minute at a rectal temperature of 39.0°C. to a glomerular filtration rate of  $38.5 \pm 10.1$  ml. per minute at a rectal temperature of 41.6°C. at the end of 4.5 hours of exposure to heat. The final dehydration averaged -1.0 percent body weight. The fall in glomerular filtration rate and renal plasma flow was not considered by the author to be due to dehydration since in a group of five hydrated dogs (with +4 percent body weight at the end) similar results were observed. No change in glomerular filtration rate or renal plasma flow occurred in either hydrated or dehydrated dogs until severe hyperthermia (greater than 41.2°C.) was present. This alteration did not occur before 3.5 to 4.0 hours of exposure to heat. Although there was a decline in the blood pressure towards the end of each exposure in both groups, the decrease in glomerular filtration rate and renal plasma flow preceded any marked fall in blood pressure. The dehydrated group exhibited an increase in hematocrit at the end of 4.5 hours exposure to heat. There was a gradual increase in plasma volume. The decrease in glomerular filtration rate and renal plasma flow demonstrated in these studies appears to the author to be directly related to the hyperthermia.

In an attempt to elucidate some of the mechanisms underlying the process of acclimatization to heat in man, Bass, Kleeman, Quinn, Henschel and Hegnauer (1259) 1955, carried out studies of the effects of prolonged heat exposure on body fluid distribution, adrenocortical activity, sweat composition and nitrogen and electrolyte metabolism. Five young men were acclimatized to heat by living and working for a

period of 14 consecutive days in a chamber maintained at 120°F. during 12 daytime hours each day, and at 100°F. during the nights. The experimental period of heat exposure was preceded by a three weeks control period at 76°F. and was followed by an 11 days recovery period at 76°F. The subjects performed standard work tasks daily and measurements were made of antipyrine, thiocyanate and T-1824 spaces, sweat concentration of sodium, chloride, potassium, nitrogen and creatinine. Sodium and electrolyte balance and indices of adrenocortical activity (circulating eosinophils and urinary 17-ketosteroids) as well as pulse rates and rectal temperature were examined. Progressive dehydration and salt deficiency were minimized by replacing sweat losses with 0.2 percent saline. The authors observed that successful acclimatization to heat was obtained within the first week. The sweat glands progressively excreted more water relative to all solutes measured during the first week with little change thereafter. Isotonic expansion of extracellular fluid in all subjects was accomplished by renal retention in the first four days of sodium and chloride in excess of that required to support sweat losses of these electrolytes. The authors concluded that the major physiological adaptation resulting in improved ability to work in the early days of acclimatization to heat are probably cardiovascular in nature. The kidney has an important role in these adaptations. It conserves sodium and chloride in excess of amounts required to compensate for sweat losses with the result that plasma and interstitial fluid volumes are isotonicly expanded. It was concluded that increased activity of the pituitary-adrenal system is not a prepotent factor in the adaptation observed in this study. That changes in the excretion of urinary adrenocortical steroids during heat stress can occur has been demonstrated by Hellman, Collins, Gray, Jones, Lunn and Weiner (1266) 1956. These investigators studied the output of urinary adrenocorticoids in 32 healthy subjects between the ages of 19 and 45 years before, during and after exposure to high environmental temperatures. While there was no significant change in the excretion of 17-hydroxycorticoids, cortisone and cortisol, or of tetrahydrocortisone and tetrahydrocortisol,

there was a significant increase in the output of aldosterone.

Respiratory changes resulting from conditions causing a rise in body temperature were studied by Barltrop (1258) 1954, in 12 subjects placed in a circulated bath. Rectal and oral temperatures were recorded. It was found that a 2°C. rise in body temperature caused an average increase of 3.8 liters in the minute volume (with a range from 0.2 to 14.2 liters). The  $P_{CO_2}$  diminished by an average of 4.8 mm. with a range from 1.9 to + 26.8 mm. Hg.

As Kanter (1269) 1953, has concluded, the kidneys in dogs exposed to heat conserve both salt and water. In these experiments the hot room was designed to maintain an air temperature of 48°C. which was sufficient to dehydrate the animals at a rate of approximately 1.0 percent body weight per hour. Fresh air was constantly drawn through a thermostatically regulated steam heating unit and blown into the hot room so that the relative humidity never attained levels that would limit evaporation. The author found no significant difference in urine flows in the hot room with or without access to water and indeed, while a dog was in negative weight balance and given water, there was no stimulation of diuresis, unless the water load exceeded the deficit. The urine chloride concentration remained below the plasma chloride concentration while the dog was in the hot room, with or without access to water. Dehydration up to 10 percent body weight had no appreciable effect on urine flows nor on the low urine chloride concentration. This low urine chloride concentration was not considered to be due to dehydration since heat by itself had a depressing effect on chloride excretion. High environmental temperature does not limit the ability of the kidneys to concentrate exogenous chloride. The urine chloride concentration also rises when the dog is removed to a cool environment. Drinking plays a major role in the regulation of imbalance in the hot room, for the addition of water alone usually suffices to restore balance rapidly. Dogs with all the available water they wish to drink failed to maintain control body weight while in the hot room, since they did not actually drink enough water during exposure to heat. The drinking pattern showed individual character-



istics. Some dogs took fewer large drafts, others many small drafts. However, the total water intake was dependent on the nature of the experiment and not on the drinking pattern.

Human heat loss during exercise at various environmental temperatures has been studied by Minard, Kitzinger and Benzinger (1278) 1957. Heat loss was recorded before, during and after standard 40 minute exercises performed by each of two subjects in a human gradient calorimeter. The subjects were exposed to five temperatures ranging from 29.5° to 21.1°C. In each test the ergometer registered 23–24 kilocalories of external work. At 29.5°C. evaporative heat loss rose steeply as work began, reaching a high plateau in 20 minutes. Radiative and convective heat loss contributed essentially nothing to the excess heat appearing during work and recovery. The total excess heat was 100 kilocalories. At 21.1°C. evaporative heat loss during work rose only slightly, the major fraction of excess heat being radiative and convective. The total excess heat was only 24 kilocalories. Thus in a cool environment heat produced during work is largely retained in the body and might serve to restore heat to tissues cooled during the preceding rest period.

For a report of physiological observations on men working under conditions of high humidity and low air movement, a paper by Ladell (1272) 1955, may be consulted. The conditions under which the studies were carried out were in a deep West African gold mine in which heat stress was avoided by frequent rests and enforced withdrawal during blasting at midshift to cooler, well-ventilated parts of the mine. Men on an eight hour shift in District A (dry bulb temperature 93. to 93.5°F.; wet bulb temperature 92 to 92.5°F.; air movement 60 to 70 ft. per minute, effective temperature 91.59°F.) and in District B (dry bulb 95.5°F.; wet bulb 93.5°F.; air movement 80 to 90 feet per minute, effective temperature 93.0°F.) and truckers (dry bulb 86°F.; wet bulb 85°F. and air movement 200 feet per minute) were studied. The rectal temperature rise of 17 men in Districts A and B was  $1.5 \pm 0.15^\circ\text{F.}$  and in 5 truckers  $1.5^\circ\text{F.}$  The mean fall in 15 men from station to surface was  $0.5 \pm 0.13^\circ\text{F.}$  The overall weight loss in 22 men was  $1.5 \text{ Kg.} \pm 0.145$ . Truckers showed a slow steady rise

in rectal temperature while the men in Districts A and B showed sharp rises during the beginning and end of the shifts with a lull or even a fall during the mid-shift period. In work tests there was no significant difference in temperature rise between novices and trained subjects. The pulse rates and sweat rates were higher in novices than in trained subjects. However, there was no evidence that the West African deep miners had an unusually high heat tolerance.

The influence of thermal environments on recovery from exposure to severe heat has been reported by Riedesel, Belding and Ross (1281) 1957. In these studies semi-nude subjects were exposed for 30 minutes in heat conditions which resulted in the production of 0.6 liters of sweat and progressive rises of rectal temperature with an average of 100.6°F., skin temperature of 100°F. and heart rates up to 140 beats per minute. Recovery from these exposures was observed during one hour of rest under four different environmental conditions:

- a) dry bulb 96°F. and vapor pressure 25 mm. Hg;
- b) dry bulb 86°F. and vapor pressure 25 mm. Hg;
- c) dry bulb 86°F. and vapor pressure 12 mm. Hg;
- d) dry bulb 76°F. and vapor pressure 12 mm. Hg.

Greater strain accompanied recovery under condition a) while the differences under the other recovery conditions were significant in only a few instances. The trends consistently indicated progressively less strain as the temperature was lower and the conditions less humid. It did not seem to matter whether the subjects were clothed or semi-nude.

With exposures to tolerable heat conditions, histopathological changes do not generally occur. Local exposure to heat, viz. testicles, definite disturbances were observed. For example, Steinberger and Dixon found that 15 minute exposures of the testicles of rats to a temperature of 45°C. produced a progressive destruction of the entire germinal epithelium, the earliest cytologic changes being observed in the spermatids.

According to Ladell (1273) 1962, a full acclimatization develops only when the environment is hotter than the body, and interference with non-evaporative heat losses causes a skin temperature rise. This does not occur in the

wet tropics, which explains the apparent anomaly of relative unacclimatization under these conditions. Full acclimatization with sweating would be of no advantage because of poor evaporation consequent on high humidity and wastage of water and salt.

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## B. PERFORMANCE

The effects of drinking water or saline, or not drinking at all, and of taking salt alone, on fully acclimatized men working in a hot and humid environment have been investigated in a number of experiments by Ladell (1286) 1955. In some tests the amount of water drunk and/or of salt taken was equated to the amounts of these substances lost in the sweat. In others saline of fixed strength was given in varying amounts. Subjective effects were more marked than were objective effects. The chances of failure to complete a given task in the heat increased with increasing water deficit. Fatigue, usually of sudden onset, was more pronounced when the water debt was high. Sweat rate tended to be lower in the men drinking saline. Abstention from water had no effect on the sweat rate until water debts of more than 2.5 liters had occurred. In this respect sweat secretion behaves similarly to urine excretion and salivation during dehydration. Thermal equilibrium was established at a higher



level in men who abstained from drinking than in those who did drink and in those not taking salt than in those taking salt. The heart rate in recovery increased with rectal temperature less rapidly when the subjects were taking salt or saline than when they were not drinking or drinking only water. In those taking salt the heart rates were faster at low rectal temperatures and slower at high rectal temperatures than in those taking water only. Exercise tolerance was better maintained by subjects when they drank water or saline than when they did not drink or took salt only.

For a paper on the upper limits of thermal stress for human subjects the report by Largent and Ashe (1287) 1958, should be consulted. These authors have studied the problem of safe upper limits of thermal stress for workmen in Indian textile mills. They have suggested a line described by 85°F./85°F. and 110°F./82°F. (dry bulb/wet bulb temperatures), as upper safe limits of thermal stress for acclimatized workmen. The location of this line appears to have been reasonably a good choice and gives relatively wide margins of safety under the conditions studied. Somewhat lower limits may be desirable for unacclimatized workmen.

The problem of exposure to raised water temperatures in underwater swimming cannot be ignored although exposure to cold in diving has received most attention. Underwater swimming in shallow tropical waters may subject personnel to water temperatures near or above skin temperature, (1290) 1956. In the actively swimming individual the metabolic heat production is high and if dissipation of this heat is impeded, considerable discomfort and physiologic derangement can result. Ordinarily heat dissipation is considerably abetted by the high conductivity of water, but if the water temperature is above skin temperature this physical factor is no longer an aid to the swimmer and body temperature must rise.

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## VII. COLD EXPOSURE PROBLEMS

### A. GENERAL PHYSIOLOGICAL EFFECTS

For a general consideration of cold exposure problems the monograph by Burton and Edholm (1297) 1955, may be consulted. This volume covers the subject fully and contains pertinent reference lists at the end of each chapter.

Regarding the effects of cooling on peripheral blood flow, evidence has been presented by Eagan (1302) 1960, that initiation of cold-induced vasodilatation is due to the intersection of vascular transmural pressure and critical closing pressure of the arteriovenous anastomoses. Eagan has reported experiments supporting the involvement of critical closing pressure on four subjects in which vascular occlusion (300 mm. Hg) of one finger was produced for various periods, and the corresponding contralateral finger served as control. It was found in these studies (with immersion of both fingers in ice water at 0°C.) that occlusion for five minutes before immersion usually, but not invariably, had no effect on cold induced vasodilatation. When an effect occurred it was one of earlier dilatation. Occlusion from five minutes before to five minutes after immersion had no effect upon the time of dilatation but the test finger tended to warm more. Occlusion from five minutes before to one minute after had a marked effect. Following release of the occlusion, an increase in finger temperature occurred and there was no phase of intense vasoconstriction subsequently. This evidence suggests that metabolites which cause reduction of critical closing pressure of the arteriovenous anastomoses and resistance vessels are not flushed out of the finger by the low blood flow existing at one minute after occlusion, so that in spite of the intense cold stimulus a true reactive hyperemia occurs.

Exposure to cold results in increased catecholamine and adrenal steroid output. Thus Arnett and Watts (1291) 1960, observed that there was a significant increase in the excretion of epinephrine and norepinephrine in the urine in male subjects exposed to a cold stress of 6.5°C. for one

hour. One hour urine samples were collected in acid immediately before and after the exposure. The increase in epinephrine excretion was more marked than that of norepinephrine, and it was concluded that the secretion of these catecholamines is involved in the chemical control of heat production during exposure to cold. Egdahl and Richards (1305) 1956, exposed unanesthetized dogs to environmental temperatures of  $-46^{\circ}$  to  $-50^{\circ}\text{C}$ . for 2–28 hours and  $-75^{\circ}$  to  $-79^{\circ}\text{C}$ . for 4–5 hours. Adrenal venous blood samples were collected prior to and during periods of cold exposure and analyzed for 17-hydroxycorticosteroids. In both temperature ranges a marked increase in adrenal steroid output occurred soon after the onset of exposure in the 10 dogs studied. In 9 of the 10 animals this response persisted for 1–3 hours after which adrenal steroid secretion returned to control pre-exposure levels despite continued cold exposure. The intravenous administration of 40 international units of ACTH produced a subsequent increase in adrenal 17-hydroxycorticosteroid output. Healthy dogs exposed to temperatures of  $-47^{\circ}\text{C}$ . for 28 hours and  $-79^{\circ}\text{C}$ . for 5 hours did not become hypothermic.

As Laties and Weiss (1325) 1959, have demonstrated, rats in a cold room will press a lever to obtain bursts of heat from a heat lamp. When working at  $2^{\circ}\text{C}$ . hypothyroid rats begin to work for heat at a steady rate earlier in a 16 hour session than do euthyroid rats. This rate is both higher and more steady for hypothyroid than for euthyroid rats. Euthyroid and hypothyroid rats working at  $5^{\circ}\text{C}$ . show a difference only in the time required to attain their steady rate. In one experiment the chronic administration of l-triiodothyronine to hypothyroid rats led to a significant decrease of lever presses as compared to the performance of normal rats. Discontinuance of l-triiodothyronine caused a gradual recovery of the high rate. The differences in this kind of behavior between hypothyroid and euthyroid animals were attributed by the authors to differences in the drive state arising from the tendency of body temperature of hypothyroid animals to decline more rapidly in the cold.

Burton, Snyder and Leach (1298) 1955–56, exposed nine human subjects lying unclothed in four experiments of 100 minutes duration at

$48^{\circ}\text{F}$ . and  $58^{\circ}\text{F}$ . with low (30 percent) and high (80 percent) relative humidity. There was a significantly greater rise of rectal temperature on exposure to cold when the humidity was low indicating a greater physiological response to vasoconstriction and a greater increase in metabolism. Shivering was considerably greater, both in incidence and severity, when the humidity was low. This was significant even at the higher temperatures. This could explain the higher thoracic temperatures in low humidity because of increased blood flow to the shivering thoracic muscles. Sensations of cold were also significantly greater in low humidity at both temperatures studied in spite of the fact that skin temperatures were not affected by humidity. Pilomotor responses were consistently seen at the lower temperatures and were not significantly related to humidity. The degree of vasoconstrictor response was estimated by calculating the insulation of the tissues. This was about maximal at both temperatures with some indication that vasoconstriction was slightly greater (except for the thorax) in the low humidities. In studies by Iampietro, Vaughan, Goldman, Kreider, Masucci and Bass (1316) 1960, healthy young men were exposed nearly nude for two hours or less to various environmental conditions (dry-bulb temperature  $90^{\circ}\text{F}$ . to  $20^{\circ}\text{F}$ .; wind speed 1, 5 and 10 mph.). Oxygen consumption was recorded at intervals during exposure. The results showed that even under conditions where no visible shivering was observed there was an increase in heat production. Exposure to very low temperatures ( $20^{\circ}\text{F}$ .) with low winds did not evoke the largest increase in heat production. The greatest mean heat production (370 Cal./hr.) was associated with the highest wind speed (10 mph.) and this value approached the maximum heat production which can be obtained by shivering (mean value about 425 Cal./hr.). Thus, increasing the wind speed has a greater impact on heat production than decreasing the dry-bulb temperature. The relationships between heat production and wind speed and heat production and dry-bulb temperature were nonlinear. Spurr, Hutt and Horwath (1336) 1957, studied skin and rectal temperatures, oxygen consumption, respiratory minute volume, carbon dioxide production, respiratory quotient and shivering in 11 experiments on 9



nude male adults before, during and after sudden exposure to a 10°C. environment. The results were compared statistically with those of experiments in an ambient temperature of -3°C. In the 10°C. environment the first tremors of shivering appeared in 6.3 minutes and generalized shivering was observed in 10.25 minutes. These times were significantly longer than those observed in the -3°C. environment. However, the average mean skin and mean body temperatures of the two groups of subjects were not significantly different at the time the first tremors of shivering and generalized shivering commenced, suggesting that the temperature receptors may sense absolute temperature as well as responding to rate of change. The respiratory minute volume, oxygen consumption and respiratory quotient showed significant increases as a result of the exposure to 10°C. and shivering. From a consideration of the data on the ventilation equivalent and percentage of carbon dioxide in expired air, it is suggested by the authors that the rise in respiratory quotient observed in both ambient temperatures was a true increase and not due entirely to overventilation on the part of the subjects. It was estimated that in the 10°C. environment shivering was approximately 5.9 percent efficient in protecting the body against heat loss. This was significantly reduced below the value of 11.6 percent observed at -3°C. It appeared, therefore, that shivering afforded relatively greater partial protection to the total body heat content in the colder environment.

The question of heat loss via the respiratory route is a critical one in low temperature operations where the inert gas used possesses qualities of high heat conductivity. In studies of oral expired air Brebbia, Goldman and Buskirk (1294) 1957, collected the water vapor in oral expired air during rest and exercise in a subarctic environment in 26 experiments on three men. Heat loss via this route was about 9 percent of the total energy expenditure and water vapor loss was directly proportional to ventilation volume.

In studies on immersion in cold water and body tissue insulation, Carlson, Hsieh, Fullington and Elsner (1300) 1958, worked with subjects in whom fat constituted 8-32 percent of the body weight. These men were immersed at 33°C., 25°C., 20°C. and in some cases at 9°C.

All experiments began with a control period at 33°C., and water temperature was then lowered to the desired level. Body insulation calculated by the Burton equation, varied directly with specific gravity, ranging from 0.10°C./cal./m.<sup>2</sup>/hr. to 0.40°C./cal./m.<sup>2</sup>/hr. However, the fraction of the body calculated to be involved as insulation was always greater than the estimated fat content. Visible shivering always was accompanied by a reduction in body insulation. These results to the authors to explain the wide variation in survival times during cold water immersion. Cannon and Keatinge (1299) 1960, found that the metabolic rate of both fat and thin young men in heat balance in water rose when the bath temperature was lowered below 33°C., although the fat men did not achieve maximum tissue insulation until the water temperature was much lower. The commonly used concept of "critical temperature" is therefore considered by the authors not valid in the case of fat men. The metabolic rate rose less in fat than in thin men when the bath temperature was lowered below 33°C. The stable rectal temperature of thin men was much lower in cold than in warm water while that of the fattest men was not. It was concluded that fat men's small metabolic response to cold was due to reflexes from the skin while in these men they were reinforced by a fall in deep temperature and consequent stimulation of deep temperature receptors. Fat men achieved higher maximum tissue insulation than thin men and could stabilize their body temperature in water down to 10-12°C. Work accelerated the fall in rectal temperature of both fat and thin men in water just too cold for them to stabilize their rectal temperature when still. Keatinge (1318, 1319) 1960, found that the fall in rectal temperature of young men immersed motionless for 30 minutes in stirred water at 15°C. varied little in successive immersions and was closely related to the subject's subcutaneous fat thickness. The falls bore relatively little relation to finger blood flow, which was always low during immersions, but both were slightly greater when the men were hot rather than cool at the time of immersion. Metabolic rates during immersion were substantially lowered by a small increase in body temperature at the time of immersion and increased by exposure to cold air, though not by moderate

exercise several hours before immersion. In the first 10 minutes of immersion the metabolic rates of thin men were slightly higher than those of fat men with a number of substantial and consistent individual differences not related to fat thickness or fall in rectal temperature. In the last 20 minutes of immersion the metabolic rates of thin men increased but those of fat men did not.

Exposure to cold in military operations raises the special issue of the practical problems of special vulnerability of particular parts of the body, such as the head and the hands. Two separate practical problems are the reduction of the total heat loss from the head, as by insulated helmets and protection from frostbite, as by face masks. These problems have been raised by Edwards and Burton (1304) 1960. Solution of both problems benefits from knowledge of the distribution of skin temperature. Temperatures in Burton and Edwards' studies were measured with thermocouples at several points on three subjects, in the steady state, at environmental temperatures of 0°C. Topographical differences were similar for the three subjects. Temperatures at a large number of points were measured on a single subject and isothermal maps were drawn from the results. These showed that the areas needing most protection from frostbite are the tip of the nose, the rim of the ears, the chin and the cheekbones. The areas of highest temperature (greatest heat loss) are those covered by the conventional insulated helmets. A face mask need not cover the area around the mouth where tactile sensitivity may make it uncomfortable. The isothermal map is correlated with the anatomical distribution of arterial blood supply. Froese and Burton (1307) 1956, have suggested from calculations that there may be excessive heat loss from the head in cold. This has been verified with a temperature gradient calorimeter made of thin Styrofoam sheets. Resistance measurement of wires covering the inside and outside surfaces of the walls gave the total flux, which by Gauss' theorem is proportional in the steady state to the magnitude of the heat source. The breath was led outside the calorimeter; thus heat loss from the head was measured on three subjects (27 runs at 14 different room temperatures). The average temperature over the inside

surfaces of the calorimeter walls ranged from 32 to -21°C. Cheek temperatures were measured in a few cases. A linear regression between heat loss and calorimeter temperature was found. The coefficient of correlation was  $0.97 \pm 11.3^\circ\text{C}$ . ( $9.4^\circ\text{F}$ .) equal to half the total resting metabolic rate. Extrapolating to zero heat loss, the 'brain temperature' was found to be 37.4°C. This temperature was used to calculate the insulation from the brain to the calorimeter wall. An average value of  $0.71 \pm 0.12$  standard clo units was obtained. The contribution of the tissue insulation to this total is estimated as 0.25 clo units. It appears therefore that there is no detectable peripheral constriction in the head during exposure to cold. This would seem to favor keeping the brain temperature normal.

Differential rates of cooling are found, the fingers being more vulnerable. Hall, Polte and Kelley (1311) 1954, carried out studies in which men wearing immersion suits were submerged in water (32-39°F.) and the hands were found to cool most rapidly. An increase of 0.6-1.1 clo units reduced this temperature drop. When the hands were kept out of the water, less rapid rates of hand cooling were observed. The feet cooled at much slower rates. The rates of average skin cooling were progressively reduced when body (trunk, arm and leg) insulation was increased from 2.3 to 3.7 and 4.7 clo units. Maximum body insulation did not alter the critical cooling rate of the immersed hands. On the basis of the rate of upper extremity and average skin temperature cooling, a body insulation of approximately 3.0-3.5 clo units is indicated for cold water (32-39°F.) immersion exposure. A metabolic increase of 54-93 percent was reported under these conditions. Immersion time was 40 minutes with 10 minutes control recording in air. In a study of finger numbness and skin temperature Mills (1331) 1956, found that the tactile discrimination of the right index finger tips of men exposed to a cold environment decreased with the skin temperature of the same area. The measure of tactile discrimination with minimum separation between two edges at which they could be discriminated is two. The log of this separation was inversely proportional to the skin temperature between 0°C. and +33°C. If the finger was rewarmed by a phase of spontaneous vaso-



dilatation, which generally developed after about 15 minutes of exposure to  $-18$  to  $-23^{\circ}\text{C}.$ , tactile discrimination recovered with the rise in skin temperature. If spontaneous rewarming did not occur at that temperature, frostbite usually ensued. Practical studies have been conducted by LeBlanc, Hildes and Héroux. In the work of these authors a group of Gaspé fishermen accustomed to cold water immersion and a group of control subjects from the same vicinity were studied to determine if the fishermen's hands were adapted to cold. With one hand immersed in cold water, the pressor response was greater in the control subjects; the fishermen maintained a higher finger temperature and complained less of pain. Heat flow from the fishermen's hands was greater than in the control group. Finger numbness was measured by a modification of Mackworth's V-test, and this was variable and not significantly different in the two groups. Skin biopsies revealed no differences in the skin thickness or cell size, but there was a significantly greater number of mast cells in the fishermen's skin. The differences between the fishermen and the control subjects may be related to repeated exposure by the former.

Tactile discrimination is impaired under cold conditions. Provine and Morton (1334) 1960, immersed the index finger of 10 subjects in water at  $0.75^{\circ}\text{C}.$  for 40 minutes. Two-edge threshold discrimination was tested during cooling of the finger and subsequent spontaneous rewarming due to cold vasodilatation. There was a marked deterioration of tactile discrimination at finger skin temperatures below about  $8^{\circ}\text{C}.$ , although the curve showing the mean decrease of numbness with increasing skin temperature was displaced relative to the curve, showing the mean increase of numbness with decreasing skin temperature. Tactile discrimination was also tested on five subjects at each of six water bath temperatures (2, 4, 6, 8, 15 and  $30^{\circ}\text{C}.$ ). At each temperature the finger was immersed for 20 minutes and the finger circulation arrested after the first five minutes. There was little impairment of two-edge discrimination after 15 to 20 minutes immersion of the finger at temperatures of  $6^{\circ}\text{C}.$  or higher. At  $4^{\circ}\text{C}.$  there was marked impairment, and at  $2^{\circ}\text{C}.$  all subjects experienced complete numbness at the test site. A further study by

Morton and Provins (1332) 1960, is also of interest. Twenty subjects exposed the index finger to air at  $-22^{\circ}\text{C}.$  and a wind speed of 300 ft./min. until the indicated skin temperature fell to  $-5^{\circ}\text{C}.$  The finger was then returned to room temperature conditions ( $19^{\circ}\text{C}.$ ) and the subject tested on each of two tasks involving tactile discrimination until the finger had fully recovered. The degree of impairment on both sensory motor tasks at a given skin temperature varied appreciably from subject to subject, although most subjects showed little impairment above  $8^{\circ}\text{C}.$  The evidence suggests that while finger numbness, as measured by Mackworth's V-test, may indicate a corresponding impairment of performance in accuracy of pressure reproduction, testing subjects on either task at normal skin temperature will have little predictive value for their relative performance after cold exposure in the present situation.

Metabolic rate tends to accelerate in human subjects exposed to cold. Thompson, Buskirk, Moore and Whedon (1338) 1960, drew attention to the fact that various methods have been applied in the past to the measurement of metabolic rate in the cold, and that these methods have been based upon interval sampling of expired gas concentrations. Although the discrete sampling approach has established sample to sample differences in metabolic rate, the moment to moment changes have not been identified. By using methods for continuous gas analysis it has been possible to delineate previously obscured features of the metabolic response (oxygen consumption) to cold. In the authors' studies young subjects varying in body composition and clothed only in shorts, were individually exposed for approximately three hours on two or more occasions to  $26^{\circ}\text{C}.$  (control environment) or  $10^{\circ}\text{C}.$  air. Notable inter-individual differences were observed in the metabolic response of these subjects to cold, both in the delay before initiation and the magnitude attained. Characteristic features of the metabolic response were its cyclic nature associated with intermittent shivering and an underlying general increase in oxygen consumption for approximately two hours following its onset. Cyclic changes in oxygen consumption were not reflected by changes in any of the measured body temperatures. The

influence of cold upon the metabolism and body temperature of wild rats, albino rats and albino rats conditioned to cold, has been reported by Krog, Monson and Irving (1323) 1955. After exposure to low temperatures for 2.5 hours the maximum metabolic effort for white rats conditioned to 5°C. occurred at -30°C., compared with -10°C. for white rats normally kept at 30°C. The difference was accounted for by the ability of cold-conditioned rats to maintain higher metabolic rates at all temperatures. Wild Norwegian rats survived lower temperatures than cold-conditioned white rats. This corresponded with the fact that wild rats could increase their metabolism in proportion to body to air temperature gradients 4.5 to 6 times over basal level as compared with a triple increase possible for white rats. The basal metabolic rate of white rats kept in cold was 60 percent above that appropriate to animals of their size. This elevation suggests that cold induced a compensatory metabolic change not normal to the species. Wild rats responded to exposure to cold in a manner normal to wild animals of cold climate. White rats deviated from the pattern of animals naturally living in cold climates. The body temperature in cold-conditioned white rats showed no appreciable fall after 2.5 hours exposure to -10°C.; the corresponding tolerance level for normal white rats was 10°C. The difference corresponded to that observed in metabolic curves, except that critical points in body temperature measurements showed up at higher temperatures because the rats were partially immobilized by thermocouples. When corresponding parts of the temperature curves were compared, the body temperature of cold-conditioned rats was shown to be a little lower than in normal animals.

Reynafarje and Chaffee (1335) 1960, have concluded that the mechanism of cold acclimatization involved a metabolic adjustment resulting in increased heat production. It is also clear that oxidation of triphosphopyridinenucleotide (TPNH) plays an important role in this acclimatization. Furthermore, the increment in activity of these reductases, which occurs only in microsomes and not in mitochondria, are regarded as the oxidative units in the cell and may signify that utilization of oxygen is not involved in the process.

Oxygen consumption and body temperature during sleep in cold environments has been studied by Kreider and Iampietro (1322) 1959. Six young soldiers slept at ambient temperatures of 25.5 to 26.0°C. (78-80°F.); 15 to 18.5°C. (60-65°F.); and -32 to -34.5°C. (-25 to -30°F). The rectal temperature and skin temperatures were recorded and mean weighted skin temperature was calculated at one-half hour intervals every night. Oxygen consumption was measured at six minute intervals on occasional nights. During sleep at a 'comfortable' temperature (25.5°C.) the rectal temperature and the mean weighted skin temperature and the oxygen consumption decreased below the resting level which was measured just before retiring. During sleep in cold environments the rectal temperature and mean skin temperature dropped to still lower levels with the lowest values recorded at an early hour of the night. The oxygen consumption during sleep in cold did not differ from values recorded during sleep at 25.5°C. The lowest values measured during sleep in the coldest environment were 35.5, 30.5 and 78 Cal./m.<sup>2</sup> for rectal temperature and mean skin temperature and body heat debt respectively. These values may represent, according to the authors, the limits of body cooling comparable with substantially continuous sleep in the cold.

The critical temperature in naked male subjects performing exercise on a bicycle ergometer in a cold room has been studied by Erikson, Krog, Anderson and Scholander (1306) 1956. Letting the subjects do just enough to avoid becoming cold, the critical temperature was found to be 26°C., confirming earlier studies.

The question of preventing immersion hypothermia is an important one. Beavers and Covino (1292) 1956, for example, have studied the effect of glycine upon immersion hypothermia. The intravenous administration of a 5 percent glycine solution was found to cause a significant increase of 34.6 minutes in the time required to lower the rectal temperature from 38 to 26°C. in dogs. Total rewarming time was decreased by 34.3 minutes in the glycine treated group. The differences in cooling and rewarming rates between the treated and nontreated animals was believed to be due to the increased heat production observed in the dogs receiving glycine.



The effect of acute cold exposure on renal function in dogs has been studied by Nungesser (1333) 1955. This author used unanesthetized trained female dogs with bladder cannuli implanted. These animals were repeatedly exposed to cold room temperatures, decreasing to lows of 4.0 to 1.8°C. for periods of one hour following 45 minute control observations at room temperatures of 22–24°C. Rectal temperatures and skin temperatures of foot and back were recorded. Renal clearances of creatinine and PAH and also water and chloride excretion were determined. Cold exposure resulted in a sharp decrease in foot temperatures and smaller decreases in back temperatures, both suggesting a decrease in peripheral blood flow. Shivering occurred in these animals and little change occurred in rectal temperatures. Usually the cold results in a decrease in renal plasma flow and chloride excretion. Glomerular filtration rate and water excretion were less frequently and less markedly decreased.

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## B. ACCLIMATIZATION

In acclimatization increased heat production caused by cold exposure is not as large as in unacclimatized subjects. This was reported by LeBlanc (1349) 1956, who observed evidence of acclimatization in soldiers exposed for four months to Arctic winter climate and who frequently experienced thermal discomfort. The subjects were exposed three times during the winter to the same standard cold stress. At the end of the winter the increased heat production caused by this standard cold exposure was not as great as in the autumn. Since the same observations have been made by various workers on laboratory animals, this result is interpreted as evidence of acclimatization to cold. Practical studies of Scholander, Hammel, Lange-Anderson and Loyning (1351) 1957, involved exposure of human subjects to conditions in the Norwegian mountains above the tree line. In September and October, eight men lived under these conditions in essentially summer clothing and with insufficient night protection. Snow and sleet were common and night temperatures were usually between 0 and +5°C. The men had enough food and were kept busy hiking, fishing and hunting. The nights were spent beneath a tarpaulin rigged as a rainproof shelter with one side open. The subjects slept naked except for socks and shorts in a single blanket sleeping bag with a hydrophobic cover. After six weeks in the field they had acquired considerable acclimatization; tests showed that they then stayed warm from head to foot all night and slept well. Heat production remained 50-60 percent higher than the basal production all night while they were asleep. Shivering, visible or detectable by electromyography, occurred frequently during sleep.



Control subjects had less elevated metabolic rates and were unable to rest and sleep due to chilling, especially of the feet. In the acclimatized men therefore an increased heat production alleviated the shell cooling from which unacclimatized people suffer. When bicycling naked in just enough cold to maintain the rectal temperature the cold acclimatized men used as much oxygen as the controls so neither during exercise nor during rest did acclimatization result in increased insulation by shell cooling. Metabolic acclimatization to cold is well known in other homeothermous systems. Davis, Johnston and Bell have carried out studies to determine the existence of physiologic acclimatization to cold in man. Subjects were exposed in a cold chamber 8 hours daily for 31 days. By the tenth day, shivering significantly decreased while heat production remained elevated 30–40 percent above basal levels throughout the period of exposure. Basal metabolic rate did not change; rectal temperature remained at pre-exposure levels for the first ten days but on the fourteenth day it fell to significantly lower values and remained there for the remainder of the experiment. Skin temperatures showed some significant fluctuations on the eighth and fourteenth days but returned to pre-exposure levels thereafter. Of the eight surface areas measured for temperature, no significant alterations took place as a result of the total period of exposure. On the basis of shivering decrease and rectal temperature change it was concluded that men can be artificially cold-acclimatized. Failure of cold-elevated heat production to decrease in the face of a significant decrease in shivering indicates to the authors the presence of nonshivering thermo-genesis in man. Peripheral and extremity temperature alterations do not take place as a result of chronic artificial cold exposure. The authors recommend that studies should be undertaken to determine the retainability of acclimatization induced by cold chamber exposure together with studies to determine the effect of heat acclimatization on cold acclimatization.

Cold acclimatization affects hepatic carbohydrate and lipid metabolism (Felts and Masoro (1343) 1959). Acclimatization of rats to low environmental temperatures was found to alter the hepatic metabolic response to fasting for one

day at 0–2°C. Liver glycogen was stabilized, fatty infiltration of the liver did not occur, and liver slices were better able to oxidize acetate and palmitate to carbon dioxide. These results provide an example of an acclimatization process occurring at the molecular level. In a previous paper Masoro and Felts (1350) 1959, pointed out that cold acclimatization greatly modifies the hepatic response of rats to fasting at low environmental temperatures. Liver glycogen almost completely disappeared in control rats fasted for 24 hours at 2°C., but is maintained at the surprisingly high level of 2 percent of net weight in cold acclimatized rats similarly treated. Of equal interest is the finding that cold acclimatization prevents the fatty infiltration of the liver that usually accompanies fasting in a cold environment. In a consideration of the effects of aging on adaptation to cold, Weiss (1352) 1959, has questioned whether the decreased ability of older and larger rats to adapt to cold is due to aging or to altered insulating properties of the tissues. Six weeks old male Holtzman rats who are depilated by clipping before cold-exposure at  $5 \pm 2^\circ\text{C}$ . show a mean survival rate of less than two days in the cold. Cold exposure for seven days before clipping allows the animals to adapt and withstand cold-exposure after clipping. One-and-one-half year-old clipped rats die soon after cold-exposure, whether pretreated with cold before clipping or not. Injection of tri-iodothyronine acetate (100 ug./100 gm. body weight, intramuscularly) on three alternate days during pretreatment with cold prolongs the survival of the older animals after clipping. Additional doses of the compound prolong maintenance in the cold when the animals are clipped twice weekly. It was suggested by the author that the older animals do not adapt as well at 5°C., but are protected in some measure from the cold by their fur. After clipping the tissues alone cannot furnish adequate insulation protection for survival. It is therefore concluded that aging does reduce the ability of the rat to adapt to cold, but adaptation in older rats can be brought about artificially by administration of thyroid hormone.

For a study of the relationship between changing levels of physical fitness and cold acclimatization, a report by Heberling and Adams (1344) 1960, may be consulted. In this study five adult

male subjects were exposed nude in a cold chamber at 10°C. for one hour before and after physical training program and following a six week winter field bivouac in interior Alaska. Body temperatures during the acute cold exposure were the criteria by which the effects of the changing levels of physical and of the "cold-acclimatizing" field encampment were judged. After the physical training program (before bivouac) the skin and extremity temperatures were significantly higher than pre-training measurements, but no differences in these values were seen after the field bivouac when physical training levels remained unchanged and the variable of cold exposure operated alone. These data confirm an earlier suggestion that these indices of acclimatization may appear as a result of chronically elevated activity levels. Dietary measurements showed equal caloric intakes in the training and bivouac phases, although formal activity requirements were discontinued in the latter test period. These data open for question the interpretation of physiological changes observed after winter bivouac or field exposure as being "cold induced".

Amongst the various metabolic changes occurring in cold adaptation is an increase in bile flow as demonstrated by Intoccia and Van Middlesworth (1346) 1958.

Immersion of personnel in cold water after shipwreck or aircraft disaster over the sea constitutes a continuing survival problem. It has not been known clearly what advice to give men about immersion in water under such conditions. Keatinge (1347) 1959, has concluded that in general men who have thick and close-fitting clothing lose heat relatively slowly in cold water and adaptation is possible. It is therefore of practical importance that personnel should if possible dress appropriately before abandoning ship or escape from a submarine.

1341. Davis, T. R. A., D. R. Johnston and F. C. Bell. Experimental cold acclimatization in man. U.S. Army. Fort Knox, Kentucky. Medical research laboratory. *Rept. no. 457*, 3 November 1960, 8 pp.

1342. Depocas, F. Metabolic response of warm and cold acclimated rats to very cold environments. *Fed. Proc.*, 1956, 15: 48.

1343. Felts, J. M. and E. J. Masoro. Effects of cold acclimation on hepatic carbohydrate and lipid metabolism. *Amer. J. Physiol.*, 1959, 197: 34-36.

1344. Heberling, E. J. and T. Adams. Relationship of changing levels of physical fitness to human cold acclimatization. *Fed. Proc.*, 1960, 19: 43.

1345. Herous, O., J. S. Hart and F. Depocas. Metabolism and muscle activity of anesthetized warm and cold acclimated rats on exposure to cold. *J. appl. Physiol.*, 1956, 9: 399-403.

1346. Intoccia, A. and L. Van Middlesworth. Bile flow increased by cold adaptation. *Fed. Proc.*, 1958, 17: 77.

1347. Keatinge, W. R. The effect of work, clothing and adaptation on the maintenance of the body temperature in water. *Gt. Brit. MRC, RNPRC, SS. Rept. R.N.P. 60.977*, S.S. 97, October 1959, 8 p.

1348. Laties, V. G. and B. Weiss. Behavior in the cold after acclimatization. *Fed. Proc.*, 1960, 19: 43.

1349. LeBlanc, J. A. Evidence and meaning of acclimatization to cold in man. *J. appl. Physiol.*, 1956, 9: 395-398.

1350. Masoro, E. J. and J. M. Felts. Effects of acclimation to cold on hepatic metabolism. *Fed. Proc.*, 1959, 18: 99.

1351. Scholander, P. F., H. T. Hammel, K. Lange-Andersen and Y. Loynning. Metabolic acclimation to cold in man. *Fed. Proc.*, 1957, 16: 114.

1352. Weiss, A. K. Effects of aging on adaptation to cold. *Fed. Proc.*, 1959, 18: 168.

### C. EFFECTS OF COLD ON PERFORMANCE

For information on the effects of exposure to cold and manual dexterity as well as other performance, papers by LeBlanc (1354) 1956, Provins and Clarke (1356) 1960, Rubin (1357) 1957, and Teichner and Kobrick (1359) 1955, may be consulted. The literature on the subject is reviewed by Provins and Clarke. Hand skin temperatures are reached at which dexterity is impaired by cold. According to LeBlanc, when the fingers alone are cooled performance of tests involving little movement of a joint may be slightly enhanced, whereas impairment is large when the joint movements are increased. This is interpreted as evidence for the hypothesis that increased viscosity of the synovial fluid is a factor in decreasing finger dexterity in the cold. However, this is not the only factor since cooling of the arm, even when the hands are kept warm, apparently causes a large decrement in finger dexterity. As Rubin has demonstrated, one of the problems in testing the effect of cold on manual dexterity is to design laboratory tasks which correlate with actual military tasks. In Rubin's study male volunteers from the Army Chemical Center performed four tasks: a nut and bolt task, a screwdriver task, a washer task and



a military task (manipulation of a kit to detect chemicals). There was no significant correlation between any of the dexterity tasks when the bare hands were used. When the hands were gloved significant correlation was found between laboratory dexterity tasks but no laboratory task correlated significantly with the military task. In these studies manual dexterity was affected by hand conditions of the experiment although temperature conditions between 25°F. and 100°F. and duration of exposure from 40 to 120 minutes had no significant effect on dexterity. In Teichner and Kobrick's studies five subjects lived in a constant temperature chamber for 41 days. For the first 16 days the temperature was held at 75°F., for the next 12 days at 55°F. and for the remaining 13 days at 75°F. Subjects were given 15 trials daily on a pursuit motor. Visual motor performance markedly and immediately deteriorated in cold and recovered gradually, but to lower levels rather than to optimal temperature conditions. The authors concluded that impairment of visual motor performance in low temperatures is the result of lowering of the final limit of performance rather than reduction of the rate of limit of learning.

1353. Carlton, P. L., R. A. Marks and B. Smith. Heat reinforced operant behavior as a function of prolonged cold exposure. U.S. Army. Fort Knox, Kentucky. Medical research laboratory. *Rept. no. 325*, 13 January 1958, 9 pp.

1354. LeBlanc, J. A. Impairment of manual dexterity in the cold. *J. appl. Physiol.*, 1956, 9: 62-64.

1355. Newton, J. M., M. Meketon, J. Roote and R. Stargel. An investigation of tracking performance in the cold with two types of controls. U.S. Army. Fort Knox, Kentucky. Medical research laboratory. *Rept. no. 324*, 6 February 1958, 13 pp.

1356. Provins, K. A. and R. S. J. Clarke. The effect of cold on manual performance. *J. occup. Med.*, 1960, 2: 169-176.

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1358. Teichner, W. H. Manual dexterity in the cold. *J. appl. Physiol.*, 1957, 11: 333-338.

1359. Teichner, W. H. and J. L. Kobrick. Effects of prolonged exposure to low temperature on visual-motor performance. *J. exp. Psychol.*, 1955, 49: 122-126.

1360. Teichner, W. H. and R. F. Wehrkamp. Visual-motor performance as a function of short duration ambient temperature. *J. exp. Psychol.*, 1954, 47: 447-450.

1361. U.S. NRC. Low temperature. pp. 23-24 in: *Status of research in underwater physiology*. U.S. NRC-CUW, Rept. 468, March 1956, 24 pp.

#### D. IMMERSION IN COLD WATER

The effects of immersion in cold water depend upon the condition of the individual at the time of immersion, the temperature of the water and the duration of exposure. The immediate effects are stimulatory upon metabolic rate, heart rate, etc., depending upon the degree of cold. The compensatory changes supervened as cold is endured. Keatinge and Evans (1364) 1960, have reported on the effect of food, alcohol and hyoscine on body temperature and reflex responses of men immersed in cold water. Neither 75 ml. of alcohol, nor a heavy meal, nor 1/100 gr. hyoscine, taken 45 minutes before immersion significantly affected the rate at which men's rectal temperatures fell during 30 minutes of immersion in water at 15°C. It was found that under these conditions the blood flow in the fingers always was reduced rapidly to low levels and that the fall was significantly less rapid after alcohol. Several of the subjects developed ventricular extrasystoles on immersion; most of these were observed after hyoscine or a heavy meal and not after alcohol. Alcohol greatly reduced the men's subjective discomfort and sensation of cold in the water. Also, alcohol usually reduced the rise in metabolic rate and the increase in heart rate during immersion. Hyoscine reduced the metabolic rates and abolished the increase in heart rates but unlike alcohol it did not affect subjective sensation of cold. For other papers on the effect of cold immersion, those by Goff, Brubach, Specht and Smith (1363) 1956; McCally and Graveline (1365) 1963, may be consulted.

1362. Beckman, E. L. Thermal protection during immersion in cold water. pp. 247-266 in: *Second symposium on underwater physiology*. Edited by C. J. Lambertsen and L. J. Greenbaum, Jr. National Research Council, Washington, D.C. N.R.C. Publication 1181, 1963, 296 pp.

1363. Goff, L. G., H. F. Brubach, H. Specht and N. Smith. Effect of total immersion at various temperatures on oxygen uptake at rest and during exercise. *J. appl. Physiol.*, 1956, 9: 59-61.

1364. Keatinge, W. R. and M. Evans. Effect of food, alcohol and hyoscine on body-temperature and reflex responses of men immersed in cold-water. *Lancet*, 1960, 2: 176-178.

1365. McCally, M. and D. E. Graveline. Urinary adrenaline and noradrenaline response to water immersion. *Fed. Proc.*, 1963, 22: 508.

## VIII. VISUAL PROBLEMS

### A. GENERAL CONSIDERATIONS

For general considerations of visual problems, reference should be made to Volume II of this Sourcebook. The reader may also consult papers by Schwartz and Sandberg (1366, 1367) 1954. These authors have determined the visual characteristics of 1064 submariners by means of Snellen wall charts and the Bausch and Lomb Ortho-Rater. From the Snellen scores the group showed peak acuity at better than 20/20 with about four percent falling below 20/30. Ortho-Rater scores were distributed normally around 20/20 with one percent falling below the equivalent of 20/30. The lateral phoria scores showed a definite tendency to exophoria at near, with 12 percent of the men exceeding five prism diopters. The visual characteristics of these 1064 submariners were also compared with those of 2354 candidates for the U.S. Naval Submarine School. With increased time in the submarine service a decrease of visual acuity for distance and for near, accompanied by a tendency toward esophoria, was found to be characteristic of the submarine population. This loss of visual efficiency may be related to the confining nature of the submarine environment.

1366. Schwartz, I. and N. E. Sandberg. Visual characteristics of the submarine population. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.57.02*, 12 June 1954, 12 pp.

1367. Schwartz, I. and N. E. Sandberg. The effect of time in submarine service on vision. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.57.03*, 30 August 1954, 9 pp.

### B. ACUITY

The references cited below may be consulted for information on visual acuity. Special mention should be made of a paper by Sweeney, Kinney and Ryan (1375) 1959. These investigators have developed a new scotopic sensitivity test at the Medical Research Laboratory. The test presents small spots of light of various sizes at a number of locations in the visual field and yields scores of the total number correctly located. A group of 108 enlisted men have been tested on this night vision test and the results show significant differences in scotopic sensitivity and a fairly normal distribution of scores. The reliability of the test measured on two consecutive days was 83. Several measures made to indicate the internal validity of the test gave positive results. In addition, various questions concerning the most efficient means of administering and scoring the test have been answered.

1368. Hillman, B. M. Relationship between stimulus size and threshold intensity in the fovea measured at four exposure times. *J. opt. Soc. Amer.*, 1958, 48: 422-428.

1369. Hillmann, B. B. Relationship between stimulus size and threshold intensity measured at four exposure times. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 22 01 20.01, Rept. no. 6*, 1958.

1370. Kinney, J. A. S. Comparison of scotopic, mesopic and photopic spectral sensitivity curves. U. S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 22 01 20.01, Rept. no. 4*, 1958.

1371. Kinney, J. A. S., E. J. Sweeney and A. P. Ryan. A new test of scotopic sensitivity. U. S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project MR005.14-2001-4, Rept. no. 4*, 3 November 1960.

1372. Luria, S. M. and I. Schwartz. Visual acuity under red vs. white illumination. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project MR 005.14-1001-10*, 14 January 1960, 8 pp.

1373. Schwartz, I. and F. L. Dimmick. Comparison of high acuity scores on Snellen and ortho-rater tests. *Amer. J. Optom.*, 1958, 35: 309-313.

1374. Sperling, H. G. and G. B. Lee. The area-intensity relationship at threshold for three stimulus durations in the human fovea. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 22 01 20*, 20 May 1957, 6 pp.

1375. Sweeney, E. J., J. A. S. Kinney and A. P. Ryan. Scotopic sensitivity test. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 23 01 20*, March 1959, 4 pp.

### C. COLOR VISION

The references cited below provide a selection of studies on color vision with particular reference to their applicability to submarine medicine. Of special interest is the report by Farnsworth (1381) 1956. This investigator has reported studies on tritanomalous vision as a threshold function. This study was undertaken to ascertain how individuals with inherited tritanopia (commonly referred to as yellow-blue color blindness) perceived colors as compared to normal individuals, using the most sensitive portion of their eye (foveal vision). It was found that subjects with tritanopia perceive colors in the



same manner and degree as do normal individuals using foveal vision. This in essence confirms previous findings that the most sensitive portion of the eye (fovea) is yellow-blue blind.

Malone (1388) 1953, has carried out a preliminary field evaluation of the relative detectability of colors for air-sea rescue. The relative detectability of a series of Munsell reds, fluorescent paints, International Orange and the standard lifeboat yellow, was the subject of this research. Observations were made from an aircraft flying at an altitude of 1000 and 500 feet and at distances of three-quarters of a mile to one and three-quarters miles from the targets. The targets were spheres of spun aluminum 34 inches in diameter which were towed in groups of five by a retriever. Observations were made during the spring and summer on sunny days with a minimum of haze. Colors from 2.5 red to 7.5 red were detected first and second a significantly greater percentage of the time than the standard lifeboat yellow. The fluorescents and International Orange also showed greater detectability than lifeboat yellow did. A photometric survey of the red lighting installation on the *USS Darter* was conducted by Moody, Squires, Lewis and Huff (1390) 1956. It was concluded that the overall red lighting installation was unsatisfactory. The general brightness level in the Attack Center was found to be too high and that in the living quarters too low. It was concluded that the purpose of red lighting in the Attack Center is to render optimal periscope viewing at night. This purpose has been defeated by the red lighting equipment installed at the time of study. Excessive brightness from non-directional overhead luminaires, together with high glare (both direct and indirect), plus white light leaks were found to be present. This lighting situation was reported to be incompatible with efficient periscope viewing. The "jewels" on panels in various compartments were uniformly too bright and too various in color to meet red light standards.

1376. Brindley, G. S. The effects on colour vision of adaptation to very bright lights. *J. Physiol.*, 1953, 122: 332-350.

1377. Dimmick, F. L. and R. E. Wienke. How red is red? *Amer. J. Psychol.*, 1958, 71: 298-304.

1378. Farnsworth, D. An introduction to the principles of color deficiency. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041. 60.01*, 8 September 1954, 15 pp.

1379. Farnsworth, D. Tritanomalous vision as a threshold function. *Farbe*, 1955, 4: 185-196.

1380. Farnsworth, D. Exposure test of fluorescent paints to sun and salt water. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 002 014.09.05*, 3 January 1956, 5 pp.

1381. Farnsworth, D. Tritanomalous vision as a threshold function. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 002 014.09, Rept. no. 3*, 1956.

1382. Farnsworth, D. and B. Hillmann. A comparison of specifications for dark adapted red. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 002 014.01.01*, 2 February 1953, 18 pp.

1383. Halsey, R. M. Identification of signal lights: I. Blue, green, white and purple: II. Elimination of the purple category. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NW 22 02 20.03, Rept. no. 1*, 22 May 1959.

1384. Hillmann, B., K. Connolly and D. Farnsworth. Color perception of small stimuli with central vision. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 002 014.09.02*, 26 October 1954, 22 pp.

1385. Katz, M. S., A. Morris and F. L. Dimmick. Effect of various durations of red adaptation on the course of subsequent dark adaptation. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.58.01*, 27 April 1954, 9 pp.

1386. Kelsey, P. A. and I. Schwartz. Nature of the limit of the color zone in perimetry. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project MR 005.14-1001.1, Rept. no. 9*, 20 October 1959.

1387. Kenney, J. A. S. Comparison of scotopic, mesopic and photopic spectral sensitivity curves. *J. opt. Soc. Amer.*, 1958, 48: 185-190.

1388. Malone, F. L. A preliminary field evaluation of the relative detectability of colors for air-sea rescue. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 002 014.09.01*, 23 November 1953, 10 pp.

1389. Moody, J. A., P. C. Squires and W. G. Lewis. Photometric survey of the red lighting installation on the *USS Seawolf*. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 002 014.08.13*, 24 September 1956, 6 pp.

1390. Moody, J. A., P. C. Squires, W. G. Lewis and J. W. Huff. Photometric survey of the red lighting installation in the *USS DARTER* (USS 576). U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 002 014.08.11*, 13 December 1956, 6 pp.

1391. Sexton, M. S., F. L. Malone and D. Farnsworth. The relative detectability of red-purples, reds, and yellow-reds, in air-sea rescue. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.35.02*, 19 March 1952, 15 pp.

1392. VonSchelling, H. Charts for measuring the effect of illumination on color vision. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.33, Rept. no. 1*, 1952.

1393. VonSchelling, H. Thickness adjustment of glass filters to given total transmittance. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.40, Rept. no. 2*, 10 March 1952.

1394. Wienke, R. E. Refractive error and the green/red ratio. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project MR 005.14-1001-1, Rept. no. 19*, 6 June 1960.

1395. Wienke, R. E. and I. Schwartz. Effect of contact lenses on the red/green ratio. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project MR 005.14-1001-1, Rept. no. 12*, 26 January 1960.

1396. Willis, M. P. and D. Farnsworth. Comparative evaluation of anomaloscopes. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.26.01*, 18 August 1952, 88 pp.

1397. U.S. Navy. Analysis of colors used in Dvorine color perception testing charts. U.S. Navy. Submarine Base, New London, Conn. Medical research department. *Project NM 003 041.10, Rept. no. 52-9*, 28 August 1952, 10 pp.

#### D. VISUAL PERFORMANCE

Reference should be made to the report of Kinney and Pratt (1403) 1954, on the effect of refractive error on acuity through binoculars. The authors made a study of visual acuity through binoculars and of the extent to which refractive errors can be corrected by adjusting the eye pieces of standard binoculars. The acuity of individuals with various types of refractive errors was measured by a liminal method using a number of dioptric settings in the binoculars. It was shown that the acuity was best at a setting indicated by the results of refractions. The acuities of a group of naval enlisted men were tested using their optimum binocular settings and a comparison was made between the performance of men who did and who did not have unaided acuity of 20/20. Persons whose unaided acuity was poor due to simple spherical errors performed as well with binoculars as those whose unaided acuity was 20/20. The type of refractive error was shown to give a more adequate prediction of the individuals who perform well with binoculars than does the 20/20 standard. It was found that astigmatism of less than one-half diopter did not impair acuity under any of the conditions tested, but larger amounts of astigmatism had a marked effect.

Attention should also be directed to an evaluation by Workman and Prickett (1409) 1957, to

determine the limitation of the visual field perimeters and distortion within this perimeter for various diving masks. The authors describe the use of the perimeter detector and measurement of visual field and distortion while wearing various diving masks. Restriction of the visual field by the diving masks evaluated was found to be from 40-50 degrees. Distortion was found only in the outer two degrees of the visual field. The results are discussed by the authors and recommendations made for masks with the least restricted visual field. The authors also outline a standard evaluation procedure for use in determining visual field restriction and distortion.

1398. Bakan, P. Discrimination decrement as a function of time in a prolonged vigil. *J. exp. Psychol.*, 1955, 50: 387-390.

1399. Colquhoun, W. P. The effect of 'unwanted' signals on performance in a vigilance task. *Ergonomics*, 1961, 4: 41-51.

1400. Hillman, B., G. B. Lee and H. G. Sperling. Brightness thresholds as a function of target contrast and retinal position. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 002 014.09.04, Rept. no. 4*, 11 July 1955.

1401. Jenkins, H. M. The effect of signal-rate on performance in visual monitoring. *Amer. J. Psychol.*, 1958, 71: 647-661.

1402. Kappauf, W. E. and W. E. Powe. Performance decrement at an audio-visual checking task. *J. exp. Psychol.*, 1959, 57: 49-56.

1403. Kinney, J. A. S. and C. H. Pratt. The effect of refractive error on acuity through binoculars. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.57, Rept. no. 1*, 2 April 1954.

1404. Squires, P. C. New digit designs for use under reflected red light of low brightness. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 22 02 20*, 20 May 1957, 11 pp.

1405. Squires, P. S. Stereo-distance identification. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 22 02 20*, 22 May 1957, 3 pp.

1406. Squires, P. C. and W. G. Lewis. Photometric survey of lighting installation on the submersible craft X-1 (SSX-1). U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 002 014.08.12*, 29 February 1956, 6 pp.

1407. Tanner, W. P., Jr. and J. A. Swets. A decision-making theory of visual detection. *Psychol. Rev.*, 1954, 61: 401-409.

1408. White, C. T. and A. Ford. Eye movements during simulated radar search. *J. opt. Soc. Amer.*, 1960, 50: 909-913.



1409. Workman, R. D. and C. M. Prickett. Visual field perimeter and distortion in diving masks. U.S. Navy. Naval Weapons Plant, EDU. *Project NS 185-005, sub task no. 4, test no. 34*, 1 February 1957, 5 pp.

#### E. NIGHT VISION AND DARK ADAPTATION

Of the references cited below, the paper by De Groot, Dodge and Smith (1412) 1952, is selected for special mention. These investigators explored the night sensitivity of the eye by using a spot of light of different brightness presented at nine points between one and 27 degrees from fixation, in each of four positions: up, down, right and left. A total of 13,000 judgments were made by three observers. Overall sensitivity was found to increase rapidly to a peak between seven and twelve degrees from fixation and then to decrease steadily into the periphery. Sensitivity in the upper, lower, nasal and temporal quadrants follow the same general pattern but with certain specific differences. The nasal quadrant had the best sensitivity over the largest area.

1410. Adams, J. A. Vigilance in the detection of low-intensity visual stimuli. *J. exp. Psychol.*, 1956, 52: 204-208.

1411. Arden, G. B. and R. A. Weale. Nervous mechanisms and dark-adaptation. *J. Physiol.*, 125: 417-426.

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1413. De Groot, S. C., J. M. Dodge and J. A. Smith. Factors in night vision sensitivity. III. The interrelation of size, brightness, and location. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.09.05*, 14 September 1953, 13 pp.

1414. Fooks, G., E. J. Sweeney and F. L. Dimmick. Pilot studies of a scotopic sensitivity test. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 23 01 20*, 14 June 1957, 7 pp.

1415. Luria, S. M. and I. Schwartz. Effect of red vs white adaptation and target illumination on the temporal course of scotopic acuity. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project MR005.14-1001-1, Rept. no. 20*, 27 December 1960.

1416. Smith, S. W. and F. L. Dimmick. Measurement of the light adaptation of the rods. *J. opt. Soc. Amer.*, 1957, 47: 391-393.

1417. Sweeney, E. J. Effect of test stimulus on the measurement of dark adaptation. *J. opt. Soc. Amer.*, 1959, 49: 667-668.

1418. Sweeney, E. J. Effect of test stimulus on measurement of dark adaptation. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 22 01 20.01, Rept. no. 8*, 8 September 1959.

#### F. UNDERWATER VISION

Miles (1421) 1962, has found that considerable absorption of light by water takes place. The light intensity is reduced to one-quarter at 15 feet and to one-eighth at 50 feet. Bathyscaphes at 1500 feet have shown that this is the limit of penetration by light from above. The type or character of the water alters these values. Colors become deceptive because light is unevenly absorbed. Blue light penetrates further than red light; the best color for artificial light under water is yellow (the mid-spectrum). The introduction of an air space between the eye and the water (as is the case in wearing face masks) causes distortion at the interface. The change in density at the interface causes refraction of all rays except the perpendicular ones. This results in the sensation of objects appearing closer than they really are, in fact they appear to be only three-quarters of their actual distance away. A report in press by Kenneth Faust constitutes an evaluation of underwater contact lenses. These lenses were developed by the Navy for underwater swimmers to obviate the use of face masks and the consequent limitation of lateral vision.

1419. Arion, M. Verres de contact pour la vision sous-marine. *Marseille méd.*, 1961, 98: 721-722.

1420. Barnard, E. E. P. Visual problems under water. *Proc. R. Soc. Med.*, 1961, 54: 755-756.

1421. Miles, S. Vision, hearing and special senses. pp. 148-157 in: *Underwater medicine*. J. B. Lippincott Co., Philadelphia, 1962, 328 pp.

#### IX. AUDITORY PROBLEMS

The reader is referred to a survey report on basic problems of underwater acoustics research published by the NRC Committee on Undersea Warfare (1457) 1950. Auditory problems in submarine operations include those pertinent to sonar operators and sound communication on a background of noise. One of the most important tasks of the sonar operator is the detection of an auditory signal which is more or less masked by a background of sound. Thus studies of masking are of major practical importance in underwater acoustics. Sound thresholds in noise (1450) 1959, and recovery times from noise and auditory fatigue (1452, 1453) 1952, are subjects of importance.

A large number of the items included in this section are reports of auditory research conducted

at the Medical Research Laboratory, U.S. Submarine Base, New London, Connecticut.

1422. Broadbent, D. E. Failure of attention in selective listening. *Gt. Brit. MRC, RNPRC. Rept. R.N.P. 52,698, O.E.S. 210, A.P.U. 168/51*, 1952, 8 pp.

1423. Broadbent, D. E. A review of multiple channel listening experiments. *Gt. Brit. MRC, RNPRC, OES. Rept. R.N.P. 55/833, O.E.S. 257*, April 1955, 9 pp.

1424. Close, P. and R. G. Ireland. Alterations in the pure tone threshold following changes in both absolute and differential pressures upon the ear. U.S. Navy. NATB, Pensacola, Fla. School of Aviation Medicine. *Project no. MR 005.13-1002, subtask 13, Rept. no. 1*, 1 November 1960, 9 pp.

1425. Faucett, R. E. The effect of Dramamine on visual and auditory acuity. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 002 015.09, Rept. no. 1*, 3 April 1953.

1426. Glorig, A. and H. P. House. A new concept in auditory screening. *Arch. Otolaryng.*, 1957, 66: 228-232.

1427. Harris, J. D. The decline of pitch discrimination with time. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.22.03*, 28 January 1952, 13 pp.

1428. Harris, J. D. An historical and critical review of loudness recruitment. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.21.07*, 20 May 1952, 47 pp.

1429. Harris, J. D. Pitch discrimination. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.22.04*, 20 June 1952, 22 pp.

1430. Harris, J. D. The roles of sensation level and of pressure in producing reversible auditory fatigue. *Laryngoscope, St. Louis*, 1954, 64: 89-97.

1431. Harris, J. D. The roles of sensation level and of sound pressure in producing reversible auditory fatigue. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.56, Rept. no. 2*, 19 April 1954.

1432. Harris, J. D. Revisions of the Navy Sonar Pitch-Memory Test. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.55.01*, 20 April 1954, 11 pp.

1433. Harris, J. D. Peak vs. total energy in thresholds for very short tones. *Acta oto-laryng., Stockh.*, 1957, 47: 134-140.

1434. Harris, J. D. The relation between the audiogram, contact-detection, and sonar operation performance. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 22 03 20.3.03*, 15 November 1957, 15 pp.

1435. Harris, J. D., H. L. Haines and C. K. Myers. A helmet-held bone conduction vibrator. *Laryngoscope, St. Louis*, 1953, 63: 998-1007.

1436. Harris, J. D., H. L. Haines and C. K. Myers. A new formula for using the audiogram to predict hearing loss for speech. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.56.07*, 24 February 1956, 28 pp.

1437. Harris, J. D., H. L. Haines and C. K. Myers. Brief-tone audiometry. *Arch. Otolaryng.*, 1958, 67: 699-713.

1438. Harris, J. D., H. L. Haines and C. K. Myers. Brief tone audiometry: temporal integration in the hypacusic. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 22 01 20.03, Rept. no. 3*, 1958.

1439. Harris, J. D., H. L. Haines and C. K. Myers. The importance of hearing at 3 KC for understanding speeded speech. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project MR 005.14-1001-2, Rept. no. 5*, 11 April 1960.

1440. Harris, J. D. and C. K. Myers. Experiments on fluctuation of auditory acuity. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003, 041.21.08*, 22 June 1952, 29 pp.

1441. Harris, J. D. and A. I. Rawnsley. The locus of short duration auditory fatigue on "adaptation." U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.56.01*, 22 January 1954.

1442. Kelsey, P. A. and A. I. Rawnsley. Adaptation of the ear to sound stimuli. The intensity time relationship. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.34.06*, 20 May 1953, 9 pp.

1443. Knight, J. J. and R. R. A. Coles. Determination of the hearing thresholds of naval recruits in terms of British and American standards. *J. acoust. Soc. Amer.*, 1960, 32: 800-804.

1444. Kohl, O. A. and W. F. Searle, Jr. Subjective and articulation tests of deep and shallow water divers communication. U.S. Navy. Naval. Weapons Plant, EDU. *Project NS 185-005, sub task no. 2, test no. 10*, 19 August 1957, 25 pp.

1445. Lawrence, M. and P. A. Yantis. Thresholds of overload in normal and pathological ears. *Arch. Otolaryng.*, 1956, 63: 66-77.

1446. Loeb, M. and E. A. Schmidt. Influence of time on task and false information on efficiency of responding to pure tones. U.S. Army. Fort Knox, Kentucky. Medical research laboratory. *Rept. no. 426*, 20 April 1960, 8 pp.

1447. Mackworth, J. F. and N. H. Mackworth. The overlapping of signals for decisions. *Amer. J. Psychol.*, 1956, 69: 26-47.

1448. O'Hare, J. J. The effect of visual stimulus on threshold of auditory acuity. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.21, Rept. no. 9*, 1952.

1449. O'Hare, J. J., J. D. Harris, R. H. Ehmer and B. H. Cohen. Some primary auditory abilities in pitch and loudness. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 22 01 20.02, Rept. no. 2*, 15 September 1959.

1450. Pettie, C. R. The loudness difference limen for tones in noise. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 22 01 20.02.01*, 7 August 1959, 5 pp.



1451. Poulton, E. C. The optimal perceptual load in a paced auditory inspection task. *Brit. J. Psychol.*, 1960, 51: 127-139.

1452. Rawnsley, A. I. and J. D. Harris. Studies in short duration auditory fatigue. IV. Recovery time. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.34.03*, 30 January 1952, 11 pp.

1453. Rawnsley, A. I. and J. D. Harris. Studies in short duration auditory fatigue. V. An investigation of the spread of fatigue within narrow frequency limits. U.S. Navy. Submarine Base, New London, Conn. Medical research department. *Project NM 003 041.34.04*, 16 May 1952, 14 pp.

1454. Rawnsley, A. I. and J. D. Harris. Comparative analysis of normal speech and speech with delayed side-tone by means of spectrograms. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.56.03*, 27 April 1954, 5 pp.

1455. Schmidt, P. H. and H. A. E. van Dishoeck. The effect on cochlear potentials of positive and negative pressures in the outer ear of the guinea-pig. *Acta physiol. pharm. neerl.*, 1959, 8: 298-299.

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1457. U.S. NRC. *A survey report on basic problems of underwater acoustics research*. U.S. NRC, Committee on Undersea Warfare, Washington, D.C., 1950, 137 pp.

1458. White, C. E. Relative evaluation of earphones by search tube microphone techniques as applied to the Permoflux PDR-8 and the Telex Twinset units. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.21.09*, 6 May 1953, 20 pp.

1459. Wing, K. G. A progress report on hypoglycemia and cochlear microphonics. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 002 015.15, Rept. no. 1*, 28 June 1954.

## X. NOISE

### A. GENERAL STUDIES

The principal noise problems in submarine operations are 1) effects of noise on hearing, 2) disturbance of performance due to noise, 3) effects of noise upon sound communication. For a good review of the subject a chapter by Parrack (1464) 1961, may be consulted. Although much of the information presented does not apply to submarine noise, Parrack's chapter is valuable not only in providing useful data but also in presenting a basic reference source.

Except for noise in the area of the sonar head nuclear powered submarines operate quietly. Fleet type submarines powered with diesel engines are noisy and the noise level varies. Harris

and White (1462) 1953, have analyzed the ambient noise in the engineroom of the *USS Harder* at six duty stations. In these studies either one, two or three engines were running at idling speed and again at full load. All conditions were run both with and without silencing hoods on the engine. The weakest reading, with one engine idling, was 108.9 db at one microphone position. The loudest reading, with three engines fullload, hoods off, was 129 db. With two engines full load, hoods on, the noise levels were always over 115 db. and ranged up to 124.2 db. With three engines full load, hoods on, the levels were about 120 db. ranging up to 125.5 db. The effect of the silencing hoods was almost negligible below 300 cycles per second, but ranged up to 5 or 6 db. at the higher frequencies. The overall noise levels were reduced on the average three db. by the silencing hoods.

1460. Burns, W. and T. S. Littler. Noise. pp. 249-267 in: *Modern trends in occupational health*. Edited by R.S.F. Schilling. Butterworth and Co., Ltd., London, 1960, 313 pp.

1461. Cox, J. R., Jr. Industrial noise and the conservation of hearing. pp. 621-693 in: *Industrial hygiene and toxicology*. Volume I. Edited by F. A. Patty, Interscience Publishers, Inc., New York, 1958, 830 pp.

1462. Harris, J. D. and C. E. White. Analysis of ambient noise in engineroom of *USS HARDER* (SS568). U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.56*, 21 December 1953, 11 pp.

1463. Lund-Iversen, L. Noise and hearing conditions on board Norwegian motor torpedo boats and submarines. *Acta oto-laryng., Stockh.*, 1957, 47: 50-63.

1464. Parrack, H. O. Effects of acoustic energy. pp. 284-323 in: *Aerospace medicine*. Edited by H. G. Armstrong, Williams and Wilkins Co., Baltimore, 1961, 633 pp.

1465. Peterson, A. P. G. and E. E. Gross, Jr. *Handbook of noise measurement*. General Radio Company, West Concord, Mass., 1960, 132 pp.

1466. Slager, U. T. Noise and vibration. pp. 241-257 in: *Space medicine*. Prentice-Hall, Inc., Englewood Cliffs, N.J., 1962, 388 pp.

1467. White, C. E. Memorandum on noise measurement. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.34*, 24 July 1953, 11 pp.

1468. Yaffe, C. D. and H. H. Jones. *Noise and hearing*. U.S. HEW, PHYS, Div. Occupational Health. Govt. Printing Office, Washington, D.C., 1961, 72 pp.

### B. PHYSIOLOGICAL AND PATHOLOGICAL EFFECTS

In a study of the threshold of aural pain to high intensity sound, Ades, Morrill and Graybiel

(1469) 1959, exposed deaf and normal human subjects monaurally to high intensity noise stimuli, including pure tone and broad band noise. The threshold of aural pain resulting from sound stimulation was found to lie in the range from 140 db and above in the normal ear, and 150 db and above in the nerve deaf ear with intact drum. There was evidence of slight interaction of hearing and pain perception. The ear drum contains the principal pain perceptive mechanism. Aural pain is without value as a warning mechanism for acoustic trauma by high intensity sound. It was found that there was considerable variation of thresholds for deaf subjects which were slightly higher than for normal persons.

According to Sackler, Weltman, Bradshaw and Jurtshuk (1489) 1959, significant endocrine changes occur in a female Wistar strain rat subjected to intense auditory stimulation with a mean intensity of 110 db at frequencies of 375–500 cps. There was a reduction in weight gain and serious changes both in endocrine weight and histologic structure of endocrine organs. There was adrenal hyperplasia, partial inhibition of ovarian activity, reduction in weight and vascularity of the uterus and loss in liver weight. Although no changes were found in either the pituitary or thyroid weight there were significant changes in the pituitary cell type and in thyroid colloid storage. The influence of high intensity noise on visual thresholds has been studied by Coleman and Krauskopf (1477) 1956. Using the psychophysical method of limits, thresholds for three visual stimuli were determined during noise and quiet conditions. Noise intensities were varied between 110 and 140 db. It was found that noise had no general effect on visual thresholds at any of the intensities used in the experiments. No differential effect of noise on the thresholds for the three visual stimuli used was demonstrated. There were consistent individual differences in visual threshold changes during noise. Absence of any demonstrable general effect of noise was due to cancellation of opposite effects in individuals. A possible factor contributing to these individual differences was investigated by showing the subjects' spurious curves, purported to represent their performance during previous sessions. The subject's performance did seem to be influenced by the fake curves,

although statistical significance was not demonstrated. Krauskopf, Coleman and Kalla (1482) 1956, investigated the effect of monaural and binaural stimulation with high intensity noise on the amplitude of eye movement occurring during fixation. It was found that 137 db noise delivered binaurally produced a significant increase in eye movement records. A partial analysis of records of the eye movements suggested that the increase in total movement was due to an increase in the high frequency fine tremor components of the record. Monaural stimulation with noise of the same intensity failed to produce any significant change in the records.

For studies on gastrointestinal reactions during a noise avoidance task a report by Davis and Berry (1478) 1961, should be consulted. Biochemical and histological changes in the cochlea of rabbits and guinea pigs have been observed after exposure to noise by Koide, Konno, Yoshikawa, Yoshida, Naakno, Nagaba and Morimoto (1481) 1960. For related studies attention is drawn to a paper by Misrahy, Arnold, Mundie, Shinabarger and Garwood (1484) 1958. Oleneva (1485) 1961, found that sound stimulation in rats produced visible disturbances in the blood vessels of the brain and changes in nerve cell dendrites and myelin fibers. These changes appeared to be localized chiefly in the medial geniculate body, and related cortex.

Palmgren (1496) 1960, has conducted an otorhinolaryngologic investigation of construction workers employed in the Stockholm underground railway from 1953 to 1957. These construction operations were carried out in caissons under excess pressure and noisy conditions. The highest pressure measured from 1.3 to 1.4 atmospheres (gauge). In addition to a general medical examination, all workers were subjected to otorhinolaryngologic investigations. Of 173 applicants accepted on the basis of the general medical examination, 24 were rejected because of changes in the ear, nose and throat region. Nine were rejected because of earlier noise damage, two because of perceptive deafness in the greater part of the frequency range from 125 to 8000 cps, ten because of deviation of the nasal septum, two because of pathologic tympanic membranes following earlier acute otitis media, and one because of inward bulging of the tym-



panic membranes after test compression at three atmospheres. Audiograms were taken in 1953 and in 1957 on all workers subjected to follow-up examination. Of those examined 21 had normal audiograms on both occasions; four were normal in 1953 but showed incipient noise damage in 1957. In 1953 24 men already presented noise damage. Eleven of these had unchanged audiograms in 1957, while six showed 15 db deterioration of hearing and seven a deterioration of more than 15 db. The total caisson working time was 1233 days. The highest measured noise level for the loading machine which produced most of the noise was 100 db at 1000 cps.

1469. Ades, H. W., S. N. Morrill and A. Graybiel. Threshold of aural pain to high intensity sound. *Aerospace Med.*, 1959, 30: 678-684.

1470. Anthony, A. Effects of noise on eosinophil levels of audiogenic-seizure-susceptible and seizure-resistant mice. *J. acoust. Soc. Amer.*, 1955, 27: 1150-1153.

1471. Anthony, A. Changes in adrenals and other organs following exposure of hairless mice to intense sound. *J. acoust. Soc. Amer.*, 1956, 28: 270-274.

1472. Anthony, A. and E. Ackerman. Effects of noise on the blood eosinophil levels and adrenals of mice. *J. acoust. Soc. Amer.*, 1955, 27: 1144-1149.

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1475. Bugard, P. L'action des bruits sur l'organisme, l'importance des effets non spécifiques. *Rev. Cps. Santé milit.*, 1960, 1: 58-72.

1476. Busnengo, E. Alcuni effetti dell'esposizione dell'uomo ai rumori e alle vibrazioni di motori a turbopropulsione. *Riv. Med. aero.*, 1959, 22: 73-84.

1477. Coleman, P. D. and J. Krauskopf. The influence of high intensity noise on visual thresholds. U.S. Army. Fort Knox, Kentucky, Medical research laboratory. *Rept. no. 222*, 22 February 1956, 26 pp.

1478. Davis, R. C. and F. Berry. Gastrointestinal reactions during a noise avoidance task. U.S. Army Office of Surgeon General. *Tech. Rept. DA-49-193-HD 2063*, July 1961, 7 pp.

1479. Hines, M. The effects of intense vibration. U.S. Army. Fort Knox, Kentucky, Medical research laboratory. *Rept. no. 358*, 10 October 1958, 57 pp.

1480. Kiang, N. Y. and M. H. Goldstein, Jr. Responses from auditory cortex to repeated bursts of noise. *Fed. Proc.*, 1956, 15: 110.

1481. Koide, Y., M. Konno, Y. Yoshikawa, M. Yoshida, Y. Nakano, M. Nagaba and M. Morimoto. Some aspects of the biochemistry of acoustic trauma. *Ann. Otol., etc., St. Louis*, 1960, 69: 661-697.

1482. Krauskopf, J., P. D. Coleman and R. Kalla. The effect of noise on eye movements. U.S. Army. Fort Knox, Kentucky, Medical research laboratory. *Rept. no. 218*, 15 February 1956, 8 pp.

1483. Lawrence, M. The effects of intense vibration. U.S. Army. Fort Knox, Kentucky, Medical research laboratory. *Rept. no. 358*, 10 October 1958, 57 pp.

1484. Misrahy, G. A., J. E. Arnold, J. R. Mundie, E. W. Shinabarger and V. P. Garwood. Genesis of endolymphatic hypoxia following acoustic trauma. *J. acoust. Soc. Amer.*, 1958, 30: 1082-1088.

1485. Oleneva, G. N. Narusheniia krovoobrashcheniia i gistopatologicheskie izmeneniia v golovnom mozgu belykh kryss pri deistvii zvuka. [Circulatory disturbances and histopathological changes in the brain of white rats due to the action of sound.] *Vestn. Otorhinolaryng., Leningr.*, 1961, 23: 34-40.

1486. Palmgren, R. Work under compression and in noisy environments. An oto-rhinolaryngologic investigation of construction workers building the Stockholm underground railway from 1953 to 1957. *Acta oto-laryng., Stockh.*, 1960, 51: 165-174.

1487. Riopelle, A. J. The effects of intense vibration. U.S. Army. Fort Knox, Kentucky, Medical research laboratory. *Rept. no. 358*, 10 October 1958, 57 pp.

1488. Ruedi, L. Different types and degrees of acoustic trauma by experimental exposure of the human and animal ear to pure tones and noise. *Ann. Otol., etc., St. Louis*, 1954, 63: 702-725.

1489. Sackler, A. M., A. S. Weltman, M. Bradshaw and P. Jurtshuk, Jr. Endocrine changes due to auditory stress. *Acta endocr., Copenhagen*, 1959, 31: 405-418.

1490. Sackler, A. M., A. S. Weltman and P. Jurtshuk, Jr. Endocrine aspects of auditory stress. *Aerospace Med.*, 1960, 31: 749-759.

1491. Schaefer, V. H., R. G. Ulmer, H. J. Link, R. H. Bouchard, D. H. Yost and R. L. Jacobs. Some behavioral and physiological studies in vibration. U.S. Army. Fort Knox, Kentucky, Medical research laboratory. *Rept. no. 389*, 12 June 1959, 28 pp.

1492. Wever, E. G. and M. Lawrence. Patterns of injury produced by overstimulation of the ear. *J. acoust. Soc. Amer.*, 1955, 27: 853-858.

## C. HEARING DEFECTS FROM EXPOSURE TO NOISE

Studies on the effect of short exposures to submarine engine noise on auditory acuity have been reported by Harris (1484) 1952. These workers presented tape-recorded noise from the engineroom of the submarine USS HARDER to Submarine School candidates at levels up to 110 db for 30 minutes. Pre- and post-exposure audiograms were collected. Levels of 105 db could be withstood easily for 30 minutes by all but the most fatigue-susceptible subjects. Levels of 100 db left residual losses sufficiently signifi-

cant to reduce speech communicability for a half-hour or more. This is a noise level commonly reached in fleet type submarines. The relation of occupational noise exposure to loss of hearing acuity has been reported by Pell (1499) 1957, who studied audiograms of 1049 males exposed to continuous and steady-state noise for five years. Over-all noise level categories included: 1) less than 75 db; 2) 75-84 db; 3) 85-90 db. These studies showed that hearing acuity of persons with normal audiograms was affected by five years occupational noise from 75 to 90 db. With Stage 1 hearing loss at the onset (no hearing loss from 250 to 2000 cps and moderate hearing loss at 4000 and/or 8000 cps) acuity was affected by exposure to 85 to 90 db, but was not affected between 75 and 84 db. With Stage 2 hearing loss at the onset (no hearing loss from 250 to 2000 cps, but severe hearing loss at 4000 and/or 8000 cps) the loss was not affected up to 90 db. It was found that hearing loss begins rapidly and proceeds slowly in its advanced stages. Persons over 45 were found to be more susceptible to traumatic hearing loss.

Webster and Solomon (1502) 1954, have studied the prevalence of hearing losses among submariners. They administered the Naval Electronics Laboratory warble tone hearing test to 1053 submariners. Hearing losses of less than 5 db could not be measured at 500 cps due to ambient noises in the training areas. At the other test frequencies (1000, 2000, 4000 and 7000 cps) any positive value of hearing loss could be measured. It was found that approximately 10 percent of all the subjects tested had high frequency hearing losses of 18 db or greater (at 4000 and 7000 cps). Comparison of hearing losses of engine men to those of all others as a function of time on the boat for each frequency showed in general that engine men had greater losses at all frequencies although there were minor reversals. The amount of loss was somewhat less than expected from previous findings. In a study of recovery following stimulation up to 140 db, Harris (1495) 1953, have three fatigue-resistant subjects stimulation at 120 to 140 db sound pressure level (750 cps) for up to ten minutes. Recovery to normal threshold at 1000 cps was studied with especial care. The shape of the recovery curve was found to depend on both the

intensity and duration of stimulation, the best predictor being a combination of both factors. Hearing loss is a linear function of stimulus duration, the function having a different slope for each stimulus intensity. To a less reliable extent, hearing loss is also a linear function of stimulus intensity when the stimulus duration is the parameter. A family of equi-noxious curves appears from these data, showing the combinations of intensity and duration which produce equally deleterious effects on the auditory threshold. These results will predict the hearing losses (at frequencies important in speech communication) by being immersed in the noise band of 600 to 1200 cps for up to ten minutes at sound pressure levels up to 140 db.

1493. Ehmer, R. H. Masking by tones vs. noise bands. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project MR 005.14-1001-2, Rept. no. 4*, 14 April 1960.

1494. Harris, J. D. Effect on auditory acuity of short exposures to submarine engine noise. U.S. Navy. Submarine Base, New London, Conn. Medical research department. *Project NM 003 041.34*, 18 December 1952, 9 pp.

1495. Harris, J. D. Recovery curves and equinoxious exposures in reversible auditory fatigue following stimulation up to 150 DB plus. *Laryngoscope, St. Louis*, 1953, 63: 660-673.

1496. Harris, J. D. Recovery curves and equinoxious exposures in reversible auditory fatigue following stimulation up to 140 DB. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.34, Rept. no. 5*, 22 November 1953,

1497. Harris, J. D. Auditory fatigue following high frequency pulse trains. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 22 03 20.2*, January 1959, 9 pp.

1498. Lawrence, M. and C. L. Blanchard. Prediction of susceptibility to acoustic trauma by determination of threshold distortion. *Univ. Mich. med. Bull.*, 1954, 20: 81-92.

1499. Pell, S. The relation of occupational noise exposure to loss of hearing acuity. *Arch. Otolaryng.*, 1957, 66: 79-92.

1500. Sataloff, J. Effect of prolonged exposure to intense noise on hearing acuity. *Arch. Otolaryng.*, 1953, 58: 62-80.

1501. Schulthess, G. V. Evaluation of hearing impairment due to industrial noise. *Arch. Otolaryng.*, 1957, 65: 512-520.

1502. Webster, J. C. and L. N. Solomon. Hearing losses among submariners and their relation to Navy auditory tasks. U.S. Navy. Naval Electronics Laboratory, San Diego, Calif., *Res. Rept. 549*, 25 October 1954, 16 pp.



#### D. EFFECTS OF NOISE ON EFFICIENCY

It has earlier been suggested on the basis of tests that aside from the engine rooms, no compartments in the fleet type submarines is noisy enough to reduce auditory acuity noticeably or to diminish psychomotor or physiological efficiency. However, it does appear that reduction in performance can result from certain intensities and durations of noise. Such a study has been reported by Broadbent (1503) 1951. Performance on noisy days under test conditions was worse than on quiet days. When lights were used the performance decrement was diminished. Broadbent (1505) 1953, has shown that under noisy conditions vigilance tasks are performed less well. Broadbent (1507) 1954, had demonstrated that a high-pitched noise causes more errors in performance than those of lower pitch, the difference being most apparent at the highest intensity of noise (100 db). In a study of the effects of noise on visual performance Broadbent (1508) 1954, found in a group of 10 subjects that impaired performance (watch keeping on a display made up of steam pressure gauges) was greater in a condition of 100 db noise as compared with 70 db. On easier tasks of watch keeping (a display of small lights) another group of 20 subjects showed no overall effect of noise. With continued exposure the performance on light watching tended to become relatively less efficient in noise so that some parts of the task were still adequately carried out while others were not. Thus noise effects are functions of individual differences, of visibility of signals and of length of performance in noise. In a further study of the effect of noise on intellectual tasks, Broadbent (1509) 1957, studied three groups of Naval ratings who worked for two sessions with a subtraction task involving a memory load. One group had both sessions in relative quiet (70 db) while the other group had the first session at 100 db and the second session in quiet. A third group had noise and quiet in the reverse order. In the first session, the noise group slowed down at solving subtraction problems as time proceeded. This was greater than in groups working under quiet conditions. Subjects who had been subjected to noise in a previous session exhibited an after-effect in the subsequent session.

Slowing down of performance with time of exposure to noise was in all groups most marked in subjects described as extroverts. Thus it was concluded by the author that intellectual work must be regarded as endangered by noises, and that there may be harmful after-effects of noise. In order to investigate whether performance is affected by short bursts of loud sound, Woodhead (1510) 1957, subjected two groups of 12 subjects each to a visual matching task with these conditions: the task ran for four minutes and four noise bursts were given at irregularly spaced intervals during that time; each of these bursts lasted for four seconds and reached a peak intensity of 100 db. One group of subjects was given more information about the test than the other; the informed group also received verbal encouragement and knowledge of results. The aim of these apparently more favorable testing conditions was to discover whether or not any performance deterioration after noise could be lessened by alerting the men to the danger and encouraging them to overcome it. It was concluded that bursts of loud noise heard by men engaged on a visual task caused immediate deterioration in the performance of most of the men, with complete recovery within the next half minute. The results demonstrated a general tendency to deteriorate immediately after noise, even when the operators were aware of this possibility and were trying to deal with it. Small variations in the task, such as a warning light, did not prevent deterioration. Prior verbal alerting and instruction to some operators enabled only a third of these to avoid the detrimental effects. In a further study Woodhead (1512) 1958, studied effects of low frequency noise bursts at 85, 95 and 115 db on a rapid decision-making task. The intention was to determine whether the unfavorable effects of a missile noise on performance might vary with the level of intensity of the noise. Tests endured for four minutes with 70 rapid decisions the rate of work varying rapidly with the changing rate of display on the screen. Four versions were given, timing the noise differently and once in silence. It was found that performance deteriorated progressively with the increased noise level. That is to say, 85 db affected work considerably less

than did 95 and 115 db. It was considered that a level of 90 db was critical.

1503. Broadbent, D. E. The twenty dials and twenty lights test under noise conditions. *Gt. Brit. MRC, RNPRC. Rept. R.N.P. 52/699, A.P.U. 160/51*, 1951, 8 pp.

1504. Broadbent, D. E. Noise, paced performance and vigilance tasks. *Gt. Brit. MRC, RNPRC. Rept. R.N.P. 52/697, O.E.S. 209, A.P.U. 165/51*, 1952, 10 pp.

1505. Broadbent, D. E. Noise, paced performance and vigilance tasks. *Brit. J. Psychol.*, 1953, 44: 295-303.

1506. Broadbent, D. E. Listening between and during practised auditory distractions. *Gt. Brit. MRC, RNPRC. Rept. R.N.P. 54/801, O.E.S. 247, A.P.U. 208*, 1954, 11 pp.

1507. Broadbent, D. E. Effects of noises of high and low pitch on behavior. *Gt. Brit. MRC, RNPRC, OES. Rept. R.N.P. 54/814, O.E.S. 253*, September 1954, 9 pp.

1508. Broadbent, D. E. Some effects of noise on visual performance. *Quart. J. exp. Psychol.*, 1954, 6: 1-5.

1509. Broadbent, D. E. An effect of noise on an 'intellectual' task. *Gt. Brit. MRC, RNPRC, OES. Rept. R.N.P. 57/892, O.E.S. 298*, July 1957, 7 pp.

1510. Woodhead, M. M. Effects of bursts of loud noise on a continuous visual task. *Gt. Brit. MRC, RNPRC, OES. Rept. R.N.P. 57/891, O.E.S. 297*, July 1957, 10 pp.

1511. Woodhead, M. M. Effects of brief loud noise on the performance of a visual task - III: Bursts of one second with a peak intensity of 110 DB. *Gt. Brit. MRC, RNPRC, OES. Rept. R.N.P. 58/914, O.E.S. 308*, February 1958, 9 pp.

1512. Woodhead, M. M. Effects of brief loud noise on the performance of a visual task - IV: An experiment with single bursts at three intensities. *Gt. Brit. MRC, RNPRC, OES. Rept. R.N.P. 58/931, O.E.S. 321*, December 1958, 4 pp.

1513. Woodhead, M. M. The effects of bursts of loud noise on a continuous visual task. *Brit. J. industr. Med.*, 1958, 15: 120-125.

### E. SOUND COMMUNICATION IN NOISE

In a study by Hoffman (1514) 1956, on the detection of signals and their attributes, a series of signals was presented against a background of noise. Listeners were required to detect these signals and to specify their separate attributes. One attribute (chopping) was produced by periodically interrupting the signal. The second attribute (modulation) consisted of a periodic change in signal band width. A given signal was either chopped, modulated, chopped and modulated or steady. It was found that though the four signals were equally detectable, detectability of the separate attributes varied as a function of their nature and number. Listeners differed in the extent to which modulation detection was adversely affected by the presence of chopping.

In all other respects differences among listeners were small.

1514. Hoffman, H. S. The detection of signals and their attributes. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.55.02*, 25 September 1956, 6 pp.

1515. Pestalozza, G. and A. Lazzaroni. Noise effect on speech perception in clinical and experimental types of deafness. *Acta oto-laryng., Stockh.*, 1954, 44: 350-358.

### F. PROTECTION AGAINST NOISE

Considerable attention has been given in the literature to the development and use of ear defender devices with the purpose of providing adequate insulation against high level sound intensities so that the magnitude of the sound reaching the ear drums is reduced to non-injurious levels. A report by Harris (1517) 1955, provides an evaluation of ear defender devices: two earplugs, four cushions and three combinations. This author has pointed out that the standard Navy ear defender (V-51R) is unsatisfactory in some respects; some people receive little protection, and the device is apparently uncomfortable for some and cannot be used with hypersensitive ears or with infected ears. A foam rubber type of earplug (impregnated with moldable wax) was found to be as effective for the average person, and to give more protection to those individuals for whom the latter apparently had little value. For individuals who were unable to tolerate any type of plug, four types of earmuffs were investigated. One of these was found to be appreciably better than the other three although this model was somewhat bulky for use in close spaces. In any situation it was found that maximum protection could be achieved by using an earplug in combination with any of several small lightweight earmuffs. For papers on conservation of hearing in occupational noise and problems of noise in industry, those by Burns and Littler (1516) and Reilly (1518) may be consulted.

1516. Burns, W. and T. S. Littler. Conservation of hearing in occupational noise. *Gt. Brit. MRC, RNPRC, OES. Rept. R.N.P. 57/881, O.E.S. 292, H.P. 7*, 1957, 7 pp.

1517. Harris, J. D. An evaluation of ear defender devices: two earplugs, four cushions and three combinations. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.56, Rept. no. 6*, 15 December 1955.

1518. Reilly, N. The problem of noise in industry. *Med. J. Aust.*, 1959, 1: 700-703.



# Biology of Very High Hydrostatic Pressures

The subject of the effects of raised hydrostatic pressure upon the activity of living cells and tissues lies at the periphery of the main interest of this Sourcebook. Nevertheless, papers in this area have been discussed in previous volumes of the sourcebook (especially Volume I). Many physical and metabolic alterations occur at very high hydrostatic pressures for example, fluids are compressed to some extent, proteins are stated to be coagulated at pressures of 5000–12,000 atmospheres and above 10,000 atmospheres the activity of enzymes become greatly diminished. Diphtheria and tetanus toxins have found to be destroyed by 13,500 atmospheres while antitoxins remain unaffected. Protozoan activity is said to cease at 400–600 atmospheres, but this is apparently reversible even after one to two days. Of the more recent literature only a few papers are here considered.

Haywood (1520) 1953, tested the hypothesis that nitrogen at high pressure exerts a general narcotic action by subjecting the fertilized eggs of the sea urchin, *Arbacia punctulata*, to a pressure of nitrogen of 61 atmospheres in the presence of air at atmospheric pressure. A series was also run with helium at the same pressure. Neither nitrogen or helium at 61 atmospheres affected the time of appearance of the first cleavage, however, as low as 2.3 atmospheres of nitrous oxide caused a definite delay of cleavage. The action of high pressure on the adenosinetriphosphatase activity of myosin has been studied by Ivanov, Mirovich and Parshina (1521) 1959. These investigators found that solutions of reprecipitated myosin lose completely their adenosinetriphosphatase activity under the influence of a pressure of 4000 atmospheres. Spyropoulos

(1522) 1956–57 studied the properties of the giant axon of the squid *Loligo pealii* at different hydrostatic pressures (14.7 to 16,000 psi). At 4,000 psi the resting potential, the membrane resistance, membrane capacity, the conduction velocity, the amplitude of the action potential and the maximal change in the membrane impedance during activity, were only slightly affected. At the same pressure, the duration of the falling phase of the action potential was increased by about 40 to 60 percent and the duration of the rising phase by about 20 to 35 percent. The duration of the membrane impedance change during activity was increased by 50 to 100 percent at 4000 psi. At about 3000 to 7000 psi fiber fired spontaneously. At pressures considerably above 5000 psi the membrane resistance decreased to about one-half to one-third the original value. The narcotizing effect upon the nerve fiber of 3 to 7 percent ethanol was partly or almost completely opposed by low temperatures or high pressures.

1519. Gershfeld, N. L. and A. M. Shanes. The influence of high hydrostatic pressure on cocaine and veratrine action in a vertebrate nerve. *J. gen. Physiol.*, 1959, 42: 647–653.

1520. Haywood, C. The cleavage times of fertilized eggs of the sea urchin, *Arbacia punctulata*, at high pressures of nitrogen, helium, and nitrous oxide. *J. cell. comp. Physiol.*, 1953, 41: 335–343.

1521. Ivanov, I. I., N. I. Mirovich and E. A. Parshina. The action of a high pressure on the adenosinetriphatase activity of myosin. *Bull. exp. Biol. Med.*, 1959, 47: 690–692.

1522. Spyropoulos, C. S. The effects of hydrostatic pressure upon the normal and narcotized nerve fiber. *J. gen. Physiol.*, 1956–57, 40: 849–857.

1523. ZoBell, C. E. Bacterial life at the bottom of the Philippine Trench. *Science*, 1952, 115: 507–508.

# Diseases and Accidents in Submarine Personnel, Divers and Compressed Air Workers

## I. EAR, NOSE AND THROAT DISTURBANCES

### A. GENERAL STUDIES OF OTORHINOLARYNGOLOGICAL DISTURBANCES

Providing they are uniformly distributed throughout the body, great pressures can be tolerated by the human organism. However, when the pressure outside is in excess of inside body air space and as long as equalization of pressure is impossible, this pressure differential causes traumatic effects including edema and effusion of blood or fluids into the space, capillary dilation or rupture of tissue. Thus, in the sinuses or the middle ear, pressure must be equalized by admission of air during descent to depth to avoid the development of destructive differences in pressure. Also during ascent the air must vent freely as pressure decreases; the latter is usually not a problem. "Squeeze" effects in the middle ear are usually taken care of by training personnel how to equalize pressure through the eustachian tubes. This is done by swallowing, cracking the jaw or by the valsalva maneuver. Temporary conditions (such as colds) which cause blockage of the eustachian tubes may prevent equalization of pressure causing otitis media and may even rupture the eardrum. The latter can occur as a result of as little as 10 feet of unequalized descent, such as may be the case if a diver falls. Blockage of the openings of the sinuses may also cause pain and trauma and exposure to pressure should be avoided during acute nose and throat conditions.

The papers listed in this section have been chosen because they give a general overview of ear, nose and throat disturbances associated with

diving and caisson operations. The reader will observe in Volume II of this Sourcebook that more space was given to ear, nose and throat disturbances than is given in the present Volume. This reflects a greater previous interest in various modalities of treatment and prevention such as irradiation therapy, dental therapy and surgical and physical procedures. Presently it is conceded that prevention is best accomplished by avoiding exposure under conditions of acute nasopharyngeal abnormality. Vasoconstrictors are of value in prevention since they may open up airway and may also be of value in treatment; if infection supervenes antibiotics are used as indicated.

1524. Bertoin, R. Evolution clinique des accidents labyrinthiques survenant chez les ouvriers travaillant en air comprimé. *Arch. Mal. prof.*, 1953, 14: 221-224.

1525. Bertrand, M. Contribution a l'étude des sinusites barotraumatiques. *Rev. Laryng., Paris*, 1954, 75: 784-813.

1526. Bruzzi, B. Sindromi otorinoiatriche nella malattia dei cassoni. *Folia med., Napoli*, 1958, 41: 780-783.

1527. Campbell, P. A. Aero-otology. Ch. XXVIII in: *Otolaryngology*. W. F. Prior Co., Inc., Hagerstown, Md. 1960, Vol. 2.

1528. Campbell, P. A. Sinus barotrauma. Ch. XII in: *Otolaryngology*. W. F. Prior Co., Inc., Hagerstown, Md. 1960, Vol. 3.

1529. Chossegros, H., L. Roche and L. Migeon. Les atteintes vestibulaires graves dans la maladie des caissons. *Arch. Mal. prof.*, 1953, 14: 211-220.

1530. Coles, R. R. A. and J. J. Knight. Aural and audiometric survey of qualified divers and submarine escape training tank instructors. *Gt. Brit. MRC, RNPRC, HeS. Rept. R.N.P. 61/1011, HeS. 29*, August 1961, 29 pp.

1531. De Vita, C. Contributo allo studio delle sinusiti barotraumatiche. *Folia med., Napoli*, 1959, 42: 781-793.

1532. Flottes, L., L. Devilla, R. Guillermin, R. Riu and B. Broussolle. La pathologie du monde du silence. *Rev. Laryng., Paris*, 1958, 79: 659-702.



1533. Guillermin, R. La codification des épreuves O.R.L. d'aptitude à la navigation aérienne et sous-marine. *Rev. Méd. nav.*, 1955, 10: 157-165.

1534. Heller, M. F. Skin diving injury. *Arch. Otolaryng.*, 1960, 72: 358-360.

1535. Jarrett, A. Reversed-ear syndrome and the mechanism of barotrauma. *Brit. med. J.*, 1961, 5250: 483-486.

1536. Jarrett, A. S. Ear injuries in divers. *J. R. nav. med. Serv.*, 1961, 47: 13-19.

1537. Jones, G. M. Pressure changes in the middle ear after altering the composition of contained gas. *Acta otolaryng.*, *Stockh.*, 1961, 53: 1-11.

1538. Jordan, L. W. Traumatic rupture of the tympanic membrane. *Laryngoscope*, 1952, 62: 615-622.

1539. Kalinin, P. I. Sravnitel'naia otsenka nekotorykh metodov opredeleniia barofunktsii ukha. [Comparative evaluation of some methods of determination of the barofunction of the ear.] *Vo.-med. Zh.*, 1961, 5: 76-77.

1540. Keller, A. P., Jr. A study of the relationship of air pressure to myringorupture. *Laryngoscope*, *St. Louis*, 1958, 68: 2015-2029.

1541. Laba, L. and J. Ruszel. About permanent injury of the ear in divers. *Bull. Inst. mar. Med. Gdansk.*, 1960, 11: 165-172.

1542. May, R. T. A preliminary report on the use of "Eskornade" in the treatment of eustachian tube block in divers under training. *J. R. nav. med. Serv.*, 1960, 46: 201-204.

1543. May, R. T. and W. M. Hollyhock. The treatment of eustachian catarrh in diving and submarine personnel with "Eskornade." *J. R. nav. med. Serv.*, 1961, 47: 143-147.

1544. Moslener, C.-D. Gehörschädigungen bei Tauchern. *Med. Mschr.*, 1961, 15: 294-297.

1545. Mungo, A. and G. Sessa. Modificazioni radiografiche dei seni paranasali nei lavoratori dei cassoni. *Folia med.*, *Napoli*, 1958, 41: 307-315.

1546. Picard, D., A. Appaix and P. Nourrit. Lésions histologiques de l'oreille interne consécutives à des barotraumatismes expérimentaux chez le Cobaye. *C.R. Soc. Biol.*, *Paris*, 1959, 153: 1230-1232.

1547. Robert, P., R. Bordes and P. Blanc. Le barotraumatisme et la surdité des aviateurs. *Rev. Cps.*, *Santé milit.*, 1960, 1: 701-712.

1548. Rózsahegyi, I. and G. Gömöri. Otologische Untersuchungen bei Caissonarbeiten. *Arch. Gewerbepath.*, 1961, 18: 384-393.

1549. Schulte, J. H. Aerotitis media and aerosinusitis in submarine trainees; a prophylactic study. *U.S. Forces med. J.*, 1957, 8: 1571-1576.

1550. Shelby, R. W. Prevention and minimization of barotraumatism injuries associated with scuba diving. *J. Amer. osteop. Ass.*, 1961, 60: 896-902.

1551. Sims, R. O. S. and S. Watson. Otitic barotrauma in divers. *Med. J. Aust.*, 1961, 1040-1041.

1552. Taylor, G. D. The otolaryngologic aspects of skin and scuba diving. *Laryngoscope*, 1959, 69: 809-858.

1553. Taylor, G. D. The otolaryngologic aspects of skin and SCUBA diving. *Trans. Amer. laryng. rhin. otol. Soc.*, 1959, 409-459.

1554. White, C. E. Report on effect of increased atmospheric pressure upon hearing. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. Project NM 002014.06.03, 21 December 1955, 6 pp.

## II. OTITIS EXTERNA THERAPY

Otitis externa is still a problem with underwater swimmers and military personnel on tropical duty. It is caused by any of a variety of bacteria and fungi. The condition may be prevented by correct hygiene of the external ear, this means essentially drying the ears well after exposure.

Fabricant (1556) 1957, has shown that the pH of the affected cutaneous surface of the external auditory meatus in otitis externa is on the alkaline side of neutral. Treatment according to this author requires converting this abnormal alkaline state to the normal physiologic acid state. In this connection Ochs (1559, 1560) 1950, has used topically aluminum acetate as a wet dressing and has added acetic acid to make a solution of about two percent strength.

For further consideration of the treatment of otitis externa as is generally practised, reference should be made to a paper by Waite quoted in Volume II of this Sourcebook (3721) 1951.

1555. Conley, J. J. Evaluation of fungous disease of the external auditory canal. *Arch. Otolaryng.*, 1948, 47: 721-745.

1556. Fabricant, N. D. The pH factor in treatment of otitis externa. *Arch. Otolaryng.*, 1957, 65: 11-12.

1557. Jenkins, B. H. Treatment of otitis externa and swimmer's ear. *J. Amer. med. Ass.*, 1961, 175: 402-404.

1558. Moretti, G. La terapia e la prevenzione delle otiti esterne nel personale subacqueo. *Ann. Med. Nav.*, 1963, 68: 443-454.

1559. Ochs, I. L. Use of vinegar as an antibiotic in the treatment of chronic middle ear disease. *Arch. Otolaryng.*, 1950, 52: 935-941.

1560. Ochs, I. L. Treatment of external otitis: a simple and effective technic. *J. Amer. med. Ass.*, 1950, 142: 1361-1362.

1561. Senturia, B. H. and C. Carruthers. Prophylaxis of external otitis; preliminary report. *Ann. Otol.*, *etc.*, *St. Louis*, 1954, 63: 97-100.

1562. Anon. External and middle ear infections. *J. Amer. med. Ass.*, 1959, 171: 554.

## III. DECOMPRESSION SICKNESS

### A. GENERAL CONSIDERATIONS

The term "decompression sickness" includes the signs, symptoms and basic underlying pathological processes caused by rapid reduction of

barometric pressure from high pressures to one atmosphere, or from any higher to any lower level of pressure. Such conditions occur in caisson work and diving. Decompression sickness is likewise a problem in rapid ascent in aircraft which are unpressurized or in which there is an explosive loss of pressure in the cabin atmosphere. The condition is characterized by pains (bends), painful breathing (chokes) and paralysis. There also may be visual and other sensory disturbances as well as convulsions and other signs of central nervous system disorder. In some cases the victim may die suddenly.

It appears that decompression has its etiology in the liberation of inert gas bubbles directly into various tissues or into the blood stream in which they are carried to find lodgment in various parts of the body. Decompression sickness occurs when the decompression rate is too rapid to allow desired gradual diffusion of excess inert gas from the tissue fluids into the blood. Only in extremely rapid decompression or in severe decompression sickness do bubbles appear in the arterial blood. With the extreme decompression rates bubbles in the returning venous blood may become lodged in the pulmonary capillaries causing the acute respiratory distress which we have referred to as "chokes". Those bubbles that pass through the pulmonary filter may enter and obstruct the capillary beds of vital organs such as the brain and the heart.

For general consideration of decompression sickness the paper by Lambertsen (1581) 1961, should be consulted. Reference is made also to the report made by Lewis and Paton (1582) 1957. This paper describes some of the factors in the pathogenesis of decompression sickness. Recommendations for lowering the rate of decompression sickness in a caisson operation are made in this paper.

1563. Agadzhanian, N. A. and D. V. Abaev. Dekompressionnye rasstroistva v usloviakh ponizhennogo atmosfernogo davleniia. (Obzor literatury.) [Decompression disorders under conditions of reduced atmospheric pressure. (Review of the literature.)] *Vo-med. Zh.*, 1960, 1: 58-62.

1564. Aver'ianov, V. A. Vliianie vysokoi temperatury vozdukh na vzniknovenie dekompressionnoi bolezni. The effect of high air temperature on the development of decompression sickness. *Patol. Fiziol. exp. Ter.*, 1961, 6: 36-39.

1565. Behnke, A. R. Decompression sickness. *Milit. Med.*, 1955, 117: 257-271.

1566. Behnke, A. R. Outline of problems of decompression and bends. pp. 50-52 in: *Proceedings of the underwater physiology symposium*. Edited by L. G. Goff, National Research Council, Washington, D.C. N.R.C. Publication 377, 1955, 153 pp.

1567. Berry, C. A. and A. H. King. Severe dysbarism in actual and simulated flight. *U.S. Forces med. J.*, 1959, 10: 3-15.

1568. Brain, W. R. Caisson disease. pp. 623-624 in: *Diseases of the nervous system*. Oxford University Press, London, 1962, 879 pp.

1569. Bucklitsch, W. and K. Pfeifer. Das Tauchens mit Pressluftgeräten. *Dtsch. Gesundheitwes.*, 1960 15: 1561-1566,

1570. Cerchia, F. Osservazioni cliniche su alcuni infortuni sul lavoro occorsi a palombari civili assistiti dal servizio sanitario di maricentrosub la spezia. *Ann. Med. Nav.*, 1953, 58: 506-526.

1571. Clamann, H. G. Decompression sickness. pp. 175-188 in: *Aerospace medicine*. Edited by H. G. Armstrong, Williams and Wilkins Co., Baltimore, 1961, 633 pp.

1572. Darling, R. C. Decompression sickness. pp. 478-480 in: *A textbook of medicine*. Edited by R. L. Cecil and R. F. Loeb, W. B. Saunders Co., Philadelphia, 1959, 1665 pp.

1573. Dewey, A. W., Jr. Decompression sickness, an emerging recreational hazard. A discussion, with an illustrative case history of an increasingly common, but not yet widely understood, sports injury. *New Engl. J. Med.*, 1962, 267: 759-765.

1574. Dewey, A. W., Jr. Decompression sickness, an emerging recreational hazard (concluded). A discussion with an illustrative case history for an increasingly common, but not yet widely understood, sports injury. *New Engl. J. Med.*, 1962, 267: 812-820.

1575. Donald, K. W. J. S. Haldane's contributions to applied physiology in the armed forces, with special reference to diving. pp. 83-91 in: *The regulation of human respiration*. Edited by D. J. C. Cunningham and B. B. Lloyd, Blackwell Scientific Publications, Oxford, 1963, 591 pp.

1576. Hansen, A. Periculum in mora. *Ugeskr. Laeg.*, 1952, 114: 33.

1577. Hunter, D. Occupational diseases with neurological symptoms and signs. *Practitioner*, 1953, 171: 48-58.

1578. Kern, J. D. The etiology and pathological physiology of decompression sickness. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. Project MR005.14-3100-2, Rept. no. 2, 15 December 1960.

1579. Kindwall, E. P. Some observations on decompression sickness. Yale University. Thesis (Med.), 1960.

1580. Lamphier, T. A., M. Spaulding, F. Boodro, J. A. Scholl, E. Tynan, R. I. Goldberg, R. Buck and J. Haggerty. Decompression illness (aerocembolism). *Industr. Med. Surg.*, 1962, 31: 239-248.



1581. Lambertsen, C. J. Harmful effects of oxygen, nitrogen, carbon dioxide and carbon monoxide. Decompression sickness. pp. 720-721 in: *Medical physiology*. Edited by P. Bard, C.V. Mosby Company, St. Louis, 1961, 1339 pp.

1582. Lewis, H. E. and W. D. M. Paton. Decompression sickness during the sinking of a caisson. A study of some factors in the pathogenesis of caisson disease. *Brit. J. industr. Med.*, 1957, 14: 5-12.

1583. Lindgren, G. *Kasunarbete och tryckfallssjuka*. Caisson work and decompression sickness. K. L. B. Boktryckeri, Stockholm, 1958, 58 pp.

1584. Meester, J. N. *Caissonziekte*. Caisson sickness. E. F. Bohn, Haarlem, 1958, 131 pp.

1585. Palmieri, V. M. *Medicina legale del cassonism*. *Folia med.*, Napoli., 1958, 41: 784-792.

1586. Perrimond-Trouchet (N). Les accidents de décompression. Définition, mécanisme, description, traitement. *Marseille méd.*, 1961, 98: 761-766.

1587. Pfrommer, J. R. Decompression sickness: The state of the art. *U.S. Forces med. J.*, 1959, 10: 1292-1298.

1588. Seusing, J. Drucklufkrankungen. *Hefte z. Unfallheilk.*, 1960, 62: 71-78.

1589. Thibault, P. Les accidents des plongeurs. *Pr. med.*, 1959, 66: 225.

1590. U.S. Air Force. Physiology of flight. USAF Manual 160-30, July 1953.

1591. U.S. Navy. Decompression. pp. 40-42 in: *Div-ing notes*. U.S. Navy, Naval Gun Factory, Washington, D.C., PRNC, DSDS-6, October 1952, 382 pp.

1592. Wünsche, O. Die Druckfallkrankheit des Höhenfliegers. *Wien. med. Wschr.*, 1956, 106: 686-689.

1593. Anon. Convegno sulla malattia dei cassoni (Napoli, 19 Gennaio 1958). *Folia med.*, Napoli, 1958, 41: 761-764.

1594. Anon. New studies of decompression sickness. *Brit. med. J.*, 1961, 5218: 45-46.

## B. CLINICAL PICTURE

For a modern succinct statement on decompression sickness reference should be made to a chapter on the subject by E. H. Lanphier, appearing as chapter VI, in *Fundamentals of Hyperbaric Medicine*, Publication No. 1298, National Academy of Sciences, National Research Council, Washington, D.C., 1966. In discussing the clinical manifestations, Lanphier considers first of all acute phenomena, namely localized pain and neurologic, pulmonary or circulatory effects. This localized pain, or bends, is present in over 90 percent of cases and is according to Lanphier the sole symptom in 95 percent of tunnel work cases. It is accompanied by other symptoms in about a third of the cases occurring in divers. Eighty-five percent of the tunnel cases exhibit pain in the legs while upper limb pain

is predominate in the divers. Pain other than in the extremities is more frequent in divers than it is in tunnelers. The neurologic pulmonary and circulatory effects are more frequent among divers. The neurological symptoms are most predominant and very variable. There is frequent vertigo in tunnel workers, while muscular weakness and sensory defects are most common in divers. It appears that paraplegia is much more frequent in compressed air workers than in divers and that neurologic manifestations in divers more commonly involve changes of consciousness, brain stem or cortical symptoms. Chokes are relatively infrequent and seem to be present in about two percent of the divers and occur with a frequency of less than one percent in tunnel workers in some studies. Signs of shock have been noted in nearly half of tunnel worker cases with other symptoms besides pain.

In addition to these major signs there are a variety of minor manifestations including itching and mottling of the skin. There is also unusual fatigue.

There may be late or chronic changes, mainly aseptic bone necrosis and enduring neurologic defects. The necrotic changes in the bone have been commonly observed among caisson and tunnel workers but have not been seen in naval divers. They are infrequently diagnosed within a year following exposure. The bone changes do not usually produce symptoms except where there is undermining of an articular surface, as for example in the head of the femur where there may be considerable pain and disability. Paraplegia due to spinal cord damage is the most common of the enduring neurological defects. Such neurological sequelae of decompression sickness most often are the result of delayed or inadequate treatment where there is acute central nervous system involvement.

The clinical features of decompression sickness during the construction of the Dartford Tunnel have been described by Golding, Griffiths, Hempleman, Paton and Walder (1599) 1960. In this operation, over a period of two years, 1200 men were employed on eight hour shifts at pressures up to 28 psi. There were 689 cases of decompression sickness out of 122,000 compressions, an incidence of 0.56 percent. The majority of cases (94.9 percent) were "simple" bends. The re-

mainder (5.1 percent) exhibited symptoms and signs other than pain and were more serious. All cases were treated successfully and no fatality or permanent disability occurred. In two serious cases cysts in the lungs were discovered and it was suggested that these gave rise to air embolism when these workers were decompressed and it may be that pulmonary defects may contribute more than hitherto believed to the pathogenesis of bends. The paper includes descriptions of other features of decompression sickness. The bends rate was higher for the back shift (3:00 p.m. and 11 p.m.) and for the night shift (11:00 p.m. to 7:00 a.m.) than it was for the day shift. In the treatment of decompression sickness it appears to be more satisfactory to use the minimum pressure required for relief of symptoms, followed by slow decompression with occasional "soaks" than to attempt to drive the causative bubbles into solution with high pressures. The decompression tables recently prescribed by the Ministry of Labour were used. Existence of acclimatization to pressure was confined; thus the bends rate may fall within two to three weeks to 0.1 percent to the incidence on the first day of exposure. Acclimatization is lost again with a "half-time" of about seven days, if a man is away from work.

Although itching is a common manifestation of decompression sickness, it has received little attention from investigators in this field. In view of its triviality in comparison with the painful maiming or even fatal consequences which can arise from diving procedures this neglect is scarcely surprising. Rashbass (1609) 1957, has justified an investigation of itching of decompression on the basis that the occurrence of itching is an indication that the dive may have been close to the borderline of safety. It appears that itching is consistently a manifestation of decompression sickness arising in a tissue whose time-constant is shorter than that of tissues responsible for the more severe effects. Thus itching is common in deep dives of short duration and absent in shallow dives of long duration. The immediate cause of itching seems to be the release of bubbles into the skin or subcutaneous tissue. Even sludging of blood may be responsible for cutaneous manifestations.

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1610. Sessa, T. Funzionalità respiratoria nei cassonisti. *Folia med., Napoli*, 1958, 41: 837-840.

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1612. Snyder, J. F. Dive reaction scale study. U.S. Navy. Naval Weapons Plant, EDU. Project NS 185-005, sub task no. 5, test no. 10, 13 March 1958, 6 pp.



1613. Viadro, M. D. and A. S. Panfilov. O dekompressionnykh rasstroistvakh u letnogo sostava v polete. [On decompression disorders in flight personnel during flight.] *Vo-med. Zh.*, 1960, 1: 62-65. *Milit. med. J.*, 1960, 1: 99-103.

### C. CASE REPORTS

Case histories of decompression sickness have been quite well documented on pages 121-137 of the first volume of this Sourcebook and on pages 161-163 of the second volume. Of the reports given below, several may be discussed in some detail. The first is a report given by Aston (1615) 1957, of a serious case of decompression sickness occurring on 27 May 1957 in a Norwegian civilian diver working from the Norwegian salvage ship *Nyhavn* on the sunken Swedish ship *Akka* off Clock Point in the Fifth of Clyde. The diver had been at a depth of 80 feet for one and a quarter hours wearing standard equipment and breathing air. According to the Royal Navy diving tables, such a dive would merit a total decompression time of 32 minutes, but owing to a breakdown in communications between the diver and his surface attendant, he was brought up in only three minutes. The patient, a 48 year old, well-built, muscular man, had had one previous attack of bends in one shoulder when he surfaced too quickly as a result of "blowing up". On the day of the reported incident his symptoms commenced relatively suddenly ten minutes after surfacing. A civilian doctor recognizing this as a case of decompression illness contacted *H.M.S. Adamant* by telephone. The patient was transferred by ambulance to a point where he was met by a medical officer and a diving officer and brought to the ship. On arrival he was placed directly in the recompression chamber. The estimated time between surfacing and entering the chamber was one and three-quarters to two hours. Initially the patient was conscious but semi-collapsed; there was pain in both lower limbs. There was also pain in the lower back, abdomen and lower half of the chest. There was vomiting and staggering. The patient had some cyanosis and respiratory distress, but these were not marked. The pulse rate was about 100. Therapeutic recompression was carried out in accordance with the Royal Navy Diving Manual. He was recompressed at 25 feet a minute to 165 feet where his symptoms were

relieved. Decompression was then started according to Table III of the Manual. When he had been at the 30 foot level for three hours he suddenly developed severe cardiac and respiratory embarrassment, becoming almost unconscious. The pulse was almost imperceptible and the rate was over 100. On recompression to 60 feet he recovered rapidly, but again felt a pain in his left lower limb, which, however, was only temporary. From this time on he was brought to the surface according to Table IV; in the last three-quarters of an hour of each of the stops at 30, 20 and 10 feet he was given oxygen. The total time spent in the chamber was 40.5 hours. In the last four hours the patient was encouraged to use his limbs gently and some massage was given. On leaving the chamber the patient was transferred to a sick bay where he was retained for 48 hours. He was then transferred to Larkfield Hospital for further observation, since it was thought possible that some permanent damage may have been done, because of the relatively sudden onset of severe symptoms and the delay before he could be recompressed. In the hospital electrocardiographic and radiological examinations were negative as was a general neurological exam. The patient returned to Norway within two weeks after admission to the hospital.

Johnson (1624) 1957, reported the case of a SCUBA diver in whom decompression sickness simulated an infectious myelitis. The author has pointed out that the popularity of skin diving is not paralleled by knowledge of the hazards and safeguards or facilities for treatment of decompression sickness and air embolism. In the case reported the diver made four consecutive dives to 90 feet for 20 minutes each, surfacing after the last dive in one minute. He had symptoms of severe pain in the left infrascapular paravertebral area, followed by numbness and tingling in arms and legs. Six to eight hours later he reported to a civilian clinic with a sensation of pressure in the back and legs. The temperature was 102°F. and there was a recent history of upper respiratory infection. The white count was 14,000. Complete paralysis of the right lower extremity followed and there was a positive Babinski bilaterally. There were no abdominal or cremasteric reflexes. There was loss of perception

of pain from the umbilicus down. The patient was unable to void. After 10 hours delay a 38 hour standard recompression procedure was undertaken. Paraplegia persisted, and in retrospect the author considered that the bubble formation was at the level of the 10th thoracic segment. McCallum and Walder (1626) 1953, have drawn attention to the importance of early and adequate treatment. A few minutes may make the difference between gross central nervous system damage and complete recovery. The authors report two cases in which there was continuing and severe disability. These cases are reported from work at the Tyne Tunnel at 34 psi. Workers were decompressed according to a fixed schedule so that tissue supersaturation pressure should fall to 18 psi before removal from the lock. In the first case an experienced man exited from the dequiment lock, disregarded decompression after two hours at 34 psi. This resulted in paralysis of both legs and bladder distension. He was recompressed to 40 psi five times and decompressed by methods prescribed for bends. A year later the patient still walked with crutches and had urinary and some fecal incontinence. In such severe cases compression should have been maintained for 24 hours. In a second case a novice had experienced two or three minor attacks of bends plus one other attack which resulted in temporary loss of the use of the legs (which should have indicated unsuitability for caisson work). After three and three-quarters hours work at 34 psi the patient developed bends during the process of correct decompression. However, decompression was then accelerated and this added to the severity of the case. The authors point out that he should have been recompressed immediately for 24 hours instead of for a much shorter and delayed period.

Richter and Behnke (1631) 1959, have reported the case of a skin diver aged 22 who developed severe spinal cord involvement after ascending too rapidly from a depth of 350 feet. There was blurring of vision, constriction of peripheral vision, numbness and loss of consciousness. After being pulled aboard the stand-by boat the victim was able to stand, but in two to three minutes had pains in the chest and in the posterior neck area as well as stabbing, hammering pain through the right arm. The legs be-

came numb. The patient was placed in a recompression chamber two hours after the accident and remained there for 48 hours. He was at three to six atmospheres for 12 hours and then was slowly decompressed for 36 hours. In efforts to combat shock he was given fluids by mouth. Hematocrit and red blood count returned to normal after 48 hours. The patient received Demerol and Meprobamate for pain and anxiety. In spite of his symptoms he was coherent, well oriented and there was no impairment of special senses. Twenty-two hours after the beginning of recompression a neurological examination showed severe generalized weakness of both lower extremities (more on the left). There was moderate, general weakness of the upper extremities; there was also ankle clonus and a positive Babinski. These and other signs and symptoms suggested multiple lesions in the spinal cord, especially in the thoracic region. There was improvement after 36 hours, but there was still considerable difficulty. One month after the accident there was residual weakness, spasticity, and sensory loss in the lower extremities. Three months after the accident the patient was able to walk unaided and there were no G.U. disturbances. Residual proprioceptive and cutaneous sensory disturbances were present. In general there was a remarkable freedom of involvement of the central nervous system in decompression sickness, even with widespread air embolism. Of all the CNS areas, the spinal cord is most susceptible to involvement and usually it is the thoracic region.

Haymaker, Johnston and Downey (1623) 1956, have reported fatal decompression sickness during jet aircraft flight. This report is concerned with two nearly identical cases of collapse during jet aircraft flight. Signs of central nervous system damage were observed in both. The clinical course was fulminant with death supervening in 11.5 and in 6 hours respectively. Pathologically the chief features were: 1) evidence of circulatory collapse; 2) the presence of intense, generalized lipemia and of fat emboli in the kidney in one case and fat emboli in the lungs and in the brain in the other; 3) a patent foramen ovale in both, with enlargement of the heart in one; 4) many foci of ischemic necrosis in the brain, indistinguishable from those due to air embolism;



and 5) acute ischemic change in the spinal cord in one of the cases. Piecing together the observations, it is postulated by the authors that the following series of events occurred: as a consequence of fairly rapid decompression fat deposits became supersaturated with gas, gas bubbles formed in fat cells, rupturing them and as a consequence fat gained access to the venous blood stream. Gas bubbles thought to have emanated from the region of fat depots were carried to the right side of the heart and thence to the lungs where many bubbles and fat emboli were filtered out. The authors concede that many may have passed the pulmonary filter. This tamponade of the pulmonary circulation produced an elevation of pulmonary blood pressure which was reflected in the right heart, enabling blood laden with bubbles to traverse the foreman ovale and enter the general circulation. Thus bubbles were carried in sufficient number to the brain to contribute to the acute circulatory collapse and death.

Pressures greater than one atmosphere have been used to treat decompression sickness occurring in flight personnel. Donnell and Norton (1620) 1960, have reported the successful use of the recompression chamber in severe decompression sickness with neurocirculatory collapse. A 39 year old obese Air Force command pilot experienced severe decompression sickness with neurocirculatory collapse following a routine refresher training course in the altitude chamber. Approximately one hour after completion of a chamber flight to 43,000 feet, the individual developed nausea and vomiting, left hemiplegia, a fall in blood pressure to shock levels and disorientation. His condition progressively deteriorated. Approximately three hours later he was placed in a recompression chamber at a nearby Naval installation. He was immediately recompressed to six atmospheres and over a period of 36 hours was gradually brought back to one atmosphere. Approximately two hours after being placed in the recompression chamber, the patient began a steady and progressive return to normal mental and physical status. Upon removal from the recompression chamber he had no essential pathological residuals. One week later the neurological examination including electroencephalograms was nor-

mal. A review of the literature by the authors indicates that this is the first altitude decompression sickness case to be treated by the use of recompression to pressures higher than one atmosphere. The authors concluded that had recompression not been available this patient would not have survived.

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1615. Aston, F. R. A case of decompression sickness. *J. R. nav. med. Serv.*, 1957, 43: 162-164.

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1618. Cotes, J. E. Decompression sickness with post-decompression collapse. *Gt. Brit., FPRC, RAF Institute of Aviation Medicine, F.P.R.C. Rept. no. 825*, April 1953, 10 pp.

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#### D. INCIDENCE, DIAGNOSIS AND PROGNOSIS

For the principle reports on this subject reference should be made to Volume II of this Sourcebook, pages 163-164. Additional references are given below.

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#### E. ETIOLOGY

It is most generally agreed that the formation of bubbles causes decompression sickness and references on this research as well as comments are to be found on pages 164-165 of Volume II of this Sourcebook. It has not yet been agreed whether or not the bubbles are usually in the blood stream or in the tissues; also controversial is the question as to whether bubbles are often or always present even if there are no symptoms. It is possible that bubbles may exist in parts of the body without giving rise to symptomatic manifestations. If so, such bubbles may cause chronic delayed damage such as aseptic bone necrosis.

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## F. PATHOLOGICAL LESIONS

On pages 142-162 of the first Volume of this Sourcebook there is given a detailed description of pathological lesions encountered in decompression sickness, including post-mortem findings, lesions of the central nervous system, lesions of the eye, ear lesions and bone and joint lesions. This treatment of the subject is supplemented by material on pages 165-167 of Volume II of the Sourcebook. This latter discussion deals principally with bone and joint lesions.

Because of the detailed attention given to pathological lesions in Volumes I and II, they will not be discussed fully here. The references that follow deal principally with bone changes. Although aseptic bone necrosis is common among caisson and tunnel workers, it is virtually not found in trained Naval divers. A report is given by Sloerdahl (1683) 1953, of aseptic necrosis of bone in three cases among 13 divers examined by X-ray. The first had aseptic necrosis of the upper end of both femors and humeri; the second had involvement of both humeri, while in the third there was necrosis of the left humerus only. Dale (1660) 1952, published two examples of professional divers with necrosis of the femoral head and of the humeral head respectively.

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## G. PREVENTION AND TREATMENT, INCLUDING PRESELECTION TESTS

### 1. GENERAL STUDIES

For a comprehensive approach to prevention and treatment of decompression sickness, a chapter by Miles (1693) 1962, should be consulted. This chapter gives the symptoms, historical background, diagnosis, treatment and prevention of decompression sickness. A comparison of the techniques of development of decompression tables for air diving is presented.

Table	Depth ft.	Duration mins.	Time at Stops 30 ft. 20 ft. 30 ft.	Total Time mins.
HALDANE	120-132	15-30	8 10 15	33
RASHBASS	130	20-30	4 9	13
CROCKER	120-130	25-30	5 20	25
U.S. NAVY	130	30	4.8 18	22.8
FRENCH	125	30	27	27

Miles gives as his opinion the view that the United States' practice of timing to the nearest minute for the stops and fractions of minutes in ascent time to the first stop is somewhat unrealistic. He believes that Crocker's five minute grading is simpler and less likely to cause error.

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### 2. DECOMPRESSION PROCEDURES

The reader may refer to reference 1728 for a description of the decompression tables in use in the U. S. Navy. These are reproduced from the *U.S. Navy Diving Manual* and are prescribed for all dives where air is the breathing medium. Figure 1 reproduces Table 1-5 U.S. Navy standard air decompression table. Figure 2 of Table 1-17, the surface decompression table using oxygen; Figure 3 is a reproduction of Table 1-18, the surface decompression table using air. The procedure for the calculation of decompression following repetitive diving is presented in table form in the Manual.

For investigative studies into the diving tables in the Royal Navy a report by Crocker (1702) 1957, may be consulted. This report (VII) describes sea trials of proposed new diving tables. These were given a stringent trial in the sea by suited divers under practical conditions. The dives finally chosen were as follows: 1) 120 feet for 30 minutes; 2) 140 feet for 30 minutes; 3) 160 feet for 25 minutes. These were the dives which effected the greatest saving of decompression time at the depths indicated. To these were added a fourth dive: 120 feet for 50 minutes, which was the longest dive at the depth for which the new stops were of shorter duration. Fifty-three dives were carried out by 23 subjects. Seven cases of decompression sickness and 17 cases of mild symptoms (not requiring recompression) occurred. They were distributed among the four test schedules as follows:



## U.S. NAVY DIVING MANUAL

Depth (ft)	Bottom time (mins)	Time to first stop	Decompression stops					Total ascent time	Repet. group
			50	40	30	20	10		
40	200						0	0.7	*
	210	0.5					2	2.5	N
	230	0.5					7	7.5	N
	250	0.5					11	11.5	O
	270	0.5					15	15.5	O
	300	0.5					19	19.5	Z
50	100						0	0.8	*
	110	0.7					3	3.7	L
	120	0.7					5	5.7	M
	140	0.7					10	10.7	M
	160	0.7					21	21.7	N
	180	0.7					29	29.7	O
	200	0.7					35	35.7	O
	220	0.7					40	40.7	Z
240	0.7					47	47.7	Z	
60	60						0	1.0	*
	70	0.8					2	2.8	K
	80	0.8					7	7.8	L
	100	0.8					14	14.8	M
	120	0.8					26	26.8	N
	140	0.8					39	39.8	O
	160	0.8					48	48.8	Z
	180	0.8					56	56.8	Z
200	0.6			1	69	70.6	Z		
70	50						0	1.2	*
	60	1.0					8	9.0	K
	70	1.0					14	15.0	L
	80	1.0					18	19.0	M
	90	1.0					23	24.0	N
	100	1.0					33	34.0	N
	110	0.8			2	41	43.8	O	
	120	0.8			4	47	51.8	O	
	130	0.8			6	52	58.8	O	
	140	0.8			8	56	64.8	Z	
	150	0.8			9	61	70.8	Z	
	160	0.8			13	72	85.8	Z	
170	0.8			19	79	98.8	Z		
80	40						0	1.3	*
	50	1.2					10	11.2	K
	60	1.2					17	18.2	L
	70	1.2					23	24.2	M
	80	1.0			2	31	34.0	N	
	90	1.0			7	39	47.0	N	
	100	1.0			11	46	58.0	O	
	110	1.0			13	53	67.0	O	
	120	1.0			17	56	74.0	Z	
	130	1.0			19	63	83.0	Z	
	140	1.0			26	69	96.0	Z	
	150	1.0			32	77	110.0	Z	
90	30						0	1.5	*
	40	1.3					7	8.3	J
	50	1.3					18	19.3	L
	60	1.3					25	26.3	M
	70	1.2			7	30	38.2	N	
	80	1.2			13	40	54.2	N	
	90	1.2			18	48	67.2	O	
	100	1.2			21	54	76.2	Z	
	110	1.2			24	61	86.2	Z	
	120	1.2			32	68	101.2	Z	
	130	1.0			5	36	74	116.0	Z
	100	25						0	1.7
30		1.5					3	4.5	I
40		1.5					15	16.5	K
50		1.3			2	24	27.3	L	
60		1.3			9	28	38.3	N	
70		1.3			17	39	57.3	O	
80		1.3			23	48	72.3	O	
90		1.2			3	23	57	84.2	Z
100		1.2			7	23	66	97.2	Z
110		1.2			10	34	72	117.2	Z
120		1.2			12	41	78	132.2	Z
110		20						0	1.8
	25	1.7					3	4.7	H
	30	1.7					7	8.7	J
	40	1.5			2	21	24.5	L	
	50	1.5			8	26	35.5	M	
	60	1.5			18	36	55.5	N	
	70	1.3			1	23	48	73.0	O
	80	1.3			7	23	57	88.3	Z
	90	1.3			12	30	64	107.3	Z
	100	1.3			15	37	72	125.3	Z

Depth (ft)	Bottom time (mins)	Time to first stop	Decompression stops					Total ascent time	Repet. group	
			50	40	30	20	10			
120	15						0	2.0	*	
	20	1.8					2	3.8	H	
	25	1.8					6	7.8	I	
	30	1.8					14	15.8	J	
	40	1.7				5	25	31.7	L	
	50	1.7				15	31	47.7	N	
	60	1.5			2	22	45	70.5	O	
	70	1.5			9	23	55	88.5	O	
	80	1.5			15	27	63	106.5	Z	
	90	1.5			19	37	74	131.5	Z	
100	1.5			23	45	80	149.5	Z		
130	10						0	2.2	*	
	15	2.0					1	3.0	F	
	20	2.0					4	6.0	H	
	25	2.0					10	12.0	J	
	30	1.8				3	18	22.8	M	
	40	1.8				10	25	36.8	N	
	50	1.7			3	21	37	62.7	O	
	60	1.7			9	23	52	85.7	Z	
	70	1.7			16	24	61	102.7	Z	
	80	1.5			3	19	35	72	130.5	Z
90	1.5			8	19	45	80	153.5	Z	
140	10						0	2.3	*	
	15	2.2					2	4.2	G	
	20	2.2					6	8.2	I	
	25	2.0				2	14	18.0	J	
	30	2.0				5	21	28.0	K	
	40	1.8			2	16	26	45.8	N	
	50	1.8			6	24	44	75.8	O	
	60	1.8			16	23	56	96.8	Z	
	70	1.7			4	19	32	68	124.7	Z
80	1.7			10	23	41	79	154.7	Z	
150	5						0	2.5	C	
	10	2.3					1	3.3	E	
	15	2.3					3	5.3	C	
	20	2.2				2	7	11.2	H	
	25	2.2				4	17	23.2	K	
	30	2.2				8	24	34.2	L	
	40	2.0			5	19	33	59.0	N	
	50	2.0			12	23	51	88.0	O	
	60	1.8			3	19	26	62	111.8	Z
70	1.8			11	19	39	75	145.8	Z	
80	1.7			1	17	19	50	84	172.7	Z
160	5						0	2.7	D	
	10	2.5					1	3.5	F	
	15	2.3				1	4	7.3	H	
	20	2.3				3	11	16.3	J	
	25	2.3				7	20	29.3	K	
	30	2.2				2	11	25	40.2	M
	40	2.2				7	23	39	71.2	N
	50	2.0			2	16	23	55	98.0	Z
60	2.0			9	19	33	69	132.0	Z	
70	1.8			1	17	22	44	80	165.8	Z
170	5						0	2.8	D	
	10	2.7					2	4.7	F	
	15	2.5				2	5	9.5	H	
	20	2.5				4	15	21.5	J	
	25	2.3				2	7	23	34.3	L
	30	2.3				4	13	26	45.3	M
	40	2.2			1	10	23	45	81.2	O
	50	2.2			5	18	23	61	109.2	Z
	60	2.0			2	15	22	37	74	152.0
70	2.0			8	17	19	51	86	183.0	Z
180	5						0	3.0	D	
	10	2.8					3	5.8	F	
	15	2.7				3	6	11.7	I	
	20	2.5			1	5	17	25.5	K	
	25	2.5			3	10	24	39.5	L	
	30	2.5			6	17	27	52.5	N	
	40	2.3			3	14	23	50	92.3	O
	50	2.2			2	9	19	30	65	127.2
60	2.2			5	16	19	44	81	167.2	Z
190	5						0	3.2	D	
	10	2.8				1	3	6.8	G	
	15	2.8				4	7	13.8	I	
	20	2.7			2	6	20	30.7	K	
	25	2.7			5	11	25	43.7	M	
	30	2.5			1	8	19	32	62.5	N
	40	2.5			8	14	23	55	102.5	O
	50	2.3			4	13	22	33	72	146.3
60	2.3			10	17	19	50	84	182.3	Z

## GENERAL PRINCIPLES OF DIVING

1**	2**	3**				4**	5**	6**	7**	1**	2**	3**				4**	5**	6**	7**
Depth in feet	Time	Time (min.) at water stops breathing air at					Time (min.) at 40' chamber stop oxygen		Approximate total decompression time (min.)	Depth in feet	Time	Time (min.) at water stops breathing air at					Time (min.) at 40' chamber stop oxygen		Approximate total decompression time (min.)
		60'	50'	40'	30'							60'	50'	40'	30'				
70	52	0	0	0	0		0		3	120	70	0	0	0	4		39		54
	90	0	0	0	0		15		24		80	0	0	0	5		46		62
	*120	0	0	0	0		23		32		90	0	0	3	7		51		72
	150	0	0	0	0		31		40		100	0	0	6	15		54		86
	180	0	0	0	0		39		48										
80	40	0	0	0	0		0		3	130	15	0	0	0	0		0		5
	70	0	0	0	0		14		23		30	0	0	0	0		12		23
	85	0	0	0	0		20		29		40	0	0	0	0		21		32
	100	0	0	0	0		26		35		50	0	0	0	3		29		43
	*115	0	0	0	0		31		40		*60	0	0	0	5		37		53
	130	0	0	0	0		37		46		70	0	0	0	7		45		63
	150	0	0	0	0		44		53		80	0	0	6	7		51		76
											90	0	0	10	12		56		90
90	32	0	0	0	0		0		4	140	13	0	0	0	0		0		6
	60	0	0	0	0		14		24		25	0	0	0	0		11		23
	70	0	0	0	0		20		30		30	0	0	0	0		15		27
	80	0	0	0	0		25		35		35	0	0	0	0		20		32
	*90	0	0	0	0		30		40		40	0	0	0	2		24		38
	100	0	0	0	0		34		44		45	0	0	0	4		29		45
	110	0	0	0	0		39		49		50	0	0	0	6		33		51
	120	0	0	0	0		43		53		*55	0	0	0	7		38		57
	130	0	0	0	0		48		58		60	0	0	0	8		43		63
											65	0	0	3	7		48		70
100	26	0	0	0	0		0		4	150	11	0	0	0	0		0		6
	50	0	0	0	0		14		24		25	0	0	0	0		13		25
	60	0	0	0	0		20		30		30	0	0	0	0		18		30
	70	0	0	0	0		26		36		35	0	0	0	0		23		39
	*80	0	0	0	0		32		42		40	0	0	3	6		27		49
	90	0	0	0	0		38		48		45	0	0	5	7		33		58
	100	0	0	0	0		44		54		*50	0	2	5	8		38		66
	110	0	0	0	0		49		59		55	2	5	9	4		44		78
110	22	0	0	0	0		0		5	160	9	0	0	0	0		0		7
	40	0	0	0	0		12		23		20	0	0	0	0		11		24
	50	0	0	0	0		19		30		25	0	0	0	0		16		29
	60	0	0	0	0		26		37		30	0	0	0	2		21		35
	*70	0	0	0	0		33		44		35	0	0	4	6		26		49
	80	0	0	0	1		40		52		40	0	3	5	8		32		62
	90	0	0	0	2		46		59		*45	3	4	8	6		38		73
	100	0	0	0	5		51		67										
120	110	0	0	0	12		54		77	170	7	0	0	0	0		0		7
	18	0	0	0	0		0		5		20	0	0	0	0		13		26
	30	0	0	0	0		9		20		25	0	0	0	0		19		32
	40	0	0	0	0		16		27		30	0	0	3	5		23		44
	50	0	0	0	0		24		35		35	0	4	4	7		29		58
	*60	0	0	0	2		32		45		*40	4	4	8	6		36		73

\*These are the optimum exposure times for each depth which represent the best balance between length of work period, safety and amount of useful work for the average diver. Exposure beyond these times is permitted only under special conditions.

\*\*Notes on columns.

Column 1. Depth—In feet, gage.

Column 2. Time—Interval from leaving the surface to leaving the bottom.

Column 3. Water stops—Time spent at tabulated stops using air. If no water stops are required use a 25 foot per minute rate of ascent to the surface. When water stops are required use a 25 foot per minute rate of ascent to first stop. Take an additional minute between stops. Use one minute for the ascent from 30 feet to the surface.

Column 4. Surface interval—The surface interval shall not exceed 5 minutes and is composed of the following elements:

(a) Time of ascent from the 30-foot water stop to the surface (1 minute).

(b) Time on surface for landing the diver on deck and undressing (not to exceed 3½ minutes).

(c) Time of descent in the recompression chamber from the surface to 40 feet (about ½ minute).

Column 5. During the period while breathing oxygen the chamber shall be ventilated.

Column 6. Surfacing—Oxygen breathing during this 2-minute period shall follow the period of oxygen breathing tabulated in Column 5 without interruption.

Column 7. Total decompression time—This includes

(a) Time of ascent from bottom to first stop at 25 feet per minute.

(b) Sum of tabulated water stops, column 2.

(c) One minute between water stops.

(d) Surface interval.

(e) Time at 40 feet in recompression chamber, column 4.

(f) Time of ascent, an additional 2 minutes, from 40 feet in the recompression chamber to the surface, column 5.

The Approximate Total Decompression Time may be shortened only by decreasing the time required to undress the diver on deck.

TABLE 1-17.—Surface decompression table using oxygen.

Figure 2



## U.S. NAVY DIVING MANUAL

Depth (ft.)	Bottom time (min.)	Time to first stop	Time at water stops			Chamber stops (air)			Total ascent time
			30	20	10	30	20	10	
40	230	0.5			3			7	10.5
	250	0.5			3			11	14.5
	270	0.5			3			15	18.5
	300	0.5			3			19	22.5
50	120	0.7			3			5	8.7
	140	0.7			3			10	13.7
	160	0.7			3			21	24.7
	180	0.7			3			29	32.7
	200	0.7			3			35	38.7
	220	0.7			3			40	43.7
	240	0.7			3			47	50.7
60	80	0.8			3			7	10.8
	100	0.8			3			14	17.8
	120	0.8			3			26	29.8
	140	0.8			3			39	42.8
	160	0.8			3			48	51.8
	180	0.8			3			56	59.8
70	200	0.7		3				3	69
	60	1.0			3			8	12.0
	70	1.0			3			14	18.0
	80	1.0			3			18	22.0
	90	1.0			3			23	27.0
	100	1.0			3			33	37.0
	110	0.8		3				3	41
	120	0.8		3				4	47
	130	0.8		3				6	52
	140	0.8		3				8	56
80	150	0.8		3				9	61
	160	0.8		3				13	72
	170	0.8		3				19	79
	50	1.2			3			10	14.2
	60	1.2			3			17	21.2
	70	1.2			3			23	27.2
	80	1.0		3				3	31
90	90	1.0		3				7	39
	100	1.0		3				11	46
	110	1.0		3				13	53
	120	1.0		3				17	56
	130	1.0		3				19	63
	140	1.0		26				26	69
	150	1.0		32				32	77
	40	1.3			3			7	11.3
100	50	1.3			3			18	22.3
	60	1.3			3			25	29.3
	70	1.2		3				7	30
	80	1.2		13				13	40
	90	1.2		18				18	48
	100	1.2		21				21	54
	110	1.2		24				24	61
	120	1.2		32				32	68
	130	1.0		5	36			36	74
110	40	1.5			3			15	19.5
	50	1.3			3			3	24
	60	1.3			3			9	28
	70	1.3			3			17	39
	80	1.3			23			23	48
	90	1.2		3	23			23	57
	100	1.2		7	23			23	66
	110	1.2		10	34			34	72
120	120	1.2		12	41			41	78
	30	1.7			3			7	11.7
	40	1.5			3			3	21
	50	1.5			3			8	26
	60	1.5			18			18	36
	70	1.5		1	23			23	48
	80	1.3		7	23			23	57
130	90	1.3		12	30			30	64
	100	1.3		15	37			37	72
	25	1.8							
	30	1.8							
140	40	1.7							
	50	1.7							
	60	1.5							
	70	1.5							
	80	1.5							
	90	1.5							
	100	1.5							
150	25	2.0							
	30	1.8							
	40	1.8							
	50	1.7							
	60	1.7							
	90	1.5							
160	20	2.2							
	25	2.0							
	30	2.0							
	40	1.8							
	50	1.8							
	60	1.8							
	70	1.7							
170	20	2.2							
	25	2.2							
	30	2.2							
	40	2.0							
	50	2.0							
	60	1.8							
180	70	1.8							
	15	2.5							
	20	2.5							
	25	2.3							
	30	2.3							
	40	2.2							
190	50	2.2							
	60	2.0							
	70	2.0							
	15	2.7							
	20	2.5							
	25	2.5							
200	30	2.5							
	40	2.3							
	50	2.2							
	60	2.2							
	15	2.8							
	20	2.7							
210	25	2.7							
	30	2.5							
	40	2.5							
	50	2.3							
	60	2.3							
	15	2.8							
220	20	2.7							
	25	2.7							
	30	2.5							
	40	2.5							
	50	2.3							
	60	2.3							
230	10	17	19	50					
	15	2.8							
	20	2.7							
	25	2.7							
	30	2.5							
	40	2.5							
240	50	2.3							
	60	2.3							
	15	2.8							
	20	2.7							
	25	2.7							
	30	2.5							
250	40	2.5							
	50	2.3							
	60	2.3							
	15	2.8							
	20	2.7							
	25	2.7							
260	30	2.5							
	40	2.5							
	50	2.3							
	60	2.3							
	15	2.8							
	20	2.7							
270	25	2.7							
	30	2.5							
	40	2.5							
	50	2.3							
	60	2.3							
	15	2.8							
280	20	2.7							
	25	2.7							
	30	2.5							
	40	2.5							
	50	2.3							
	60	2.3							
290	10	17	19	50					
	15	2.8							
	20	2.7							
	25	2.7							
	30	2.5							
	40	2.5							
300	50	2.3							
	60	2.3							
	15	2.8							
	20	2.7							
	25	2.7							
	30	2.5							
310	40	2.5							
	50	2.3							
	60	2.3							
	15	2.8							
	20	2.7							
	25	2.7							
320	30	2.5							
	40	2.5							
	50	2.3							
	60	2.3							
	15	2.8							
	20	2.7							
330	25	2.7							
	30	2.5							
	40	2.5							
	50	2.3							
	60	2.3							
	15	2.8							
340	20	2.7							
	25	2.7							
	30	2.5							
	40	2.5							
	50	2.3							
	60	2.3							
350	10	17	19	50					
	15	2.8							
	20	2.7							
	25	2.7							
	30	2.5							
	40	2.5							
360	50	2.3							
	60	2.3							
	15	2.8							
	20	2.7							
	25	2.7							
	30	2.5							
370	40	2.5							
	50	2.3							
	60	2.3							
	15	2.8							
	20	2.7							
	25	2.7							
380	30	2.5							
	40	2.5							
	50	2.3							
	60	2.3							
	15	2.8							
	20	2.7							
390	25	2.7							
	30	2.5							
	40	2.5							
	50	2.3							
	60	2.3							
	15	2.8							
400	20	2.7							
	25	2.7							
	30	2.5							
	40	2.5							
	50	2.3							

<i>Test schedule</i>	<i>Cases of bends</i>	<i>Minor symptoms</i>	<i>No. of dives</i>
1. 120 ft. for 30 min.	2	4	20
2. 120 ft. for 50 min.	2	4	14
3. 140 ft. for 30 min.	1	5	11
4. 160 ft. for 25 min.	2	4	8

It is concluded by the author that the margin of safety in the more critical dives is too narrow for the tables to be adopted by the services in their entirety. Crocker has given a further report on the revised tables (1703). Kiessling and Duffner (1712) 1960, reported the development of a test to determine the adequacy of decompression following a dive. In these studies Navy divers performed working dives in a pressure tank for 30 minutes at simulated depths of 90, 110 and 125 feet. The work consisted of swimming on an ergometer and weight lifting. Following the dive the subjects were decompressed to atmospheric pressure at a rate of 60 feet per minute. Upon surfacing the subjects observed the following routine: 0-15 minutes, unsupervised activity; 15-45 minutes, exercise (five deep knee bends and five push-ups every five minutes); 45-50 minutes, ascent to simulated altitude of 18,000 feet; 50-105 minutes, at altitude exercising (ten deep knee bends every five minutes). The times of occurrence of any signs or symptoms of decompression sickness were recorded. The experiment was terminated when the subject could no longer tolerate his symptoms. These three exposures were considered to represent different decompression sickness hazard levels and hence were designated as GREEN, YELLOW and RED dives. The following mean endpoints in terms of time at altitude were observed: GREEN 47.5, YELLOW 21.4 and RED 7.2. Statistical analysis demonstrated that these mean differences did not occur by chance, but as a product of the experimental conditions. The authors concluded that this procedure will quantitatively measure the adequacy of decompression.

For studies of decompression and inert gas-oxygen mixtures in the U.S. Navy a report by Workman (1722) 1963, should be consulted.

Davidson and Taylor (1704) 1952, have carried out animal and human experiments on surface decompression procedures. Animal studies have shown that surface decompression is likely

to be successful for depths down to 300 feet if a modified technique is used. A depth of 190 feet had been the previous limit. Experiments on human subjects confirmed the safety of the method down to 230 feet. For a report of sea trials on the surface decompression routine, Mackay's paper (1716) 1958, may be perused. Two hundred and ten dives were carried out to test a new routine of surface decompression in sheltered sea waters with an overall incidence of major decompression sickness of 4.29 percent. The range of depths for the dives was 80 to 180 feet and the duration of the dives was chosen to test the tables more fully. These dives were work dives, consisting of bottom sorties of linkcutting. Rate of descent was precisely regulated to one foot per second with decompression carried out in a chamber aboard ship. The diver was brought from the bottom immediately to the surface, placed in the chamber and recompressed to a depth 30 feet below the dive depth. (The time required to accomplish should not exceed five minutes.) The chamber was kept at the 30+ depth for five minutes and then decompression was carried out as scheduled for a dive of ten minutes longer than the actual dive performed. One minute was used to get to the first new stop. The author recommended that the routine for surface decompression be accepted to replace the Royal Navy Diving Manual routine. For an additional paper on surface decompression, that by Workman (1721) 1957, may be consulted. Here a method is reported on surface decompression for diving to depths of 190 feet, employing modified standard air decompression tables. Essentially the procedure is to bring the diver to the surface following minimal decompression in the water and to recompress him in a chamber within 3.5 minutes. The excess inert gas tension can be tolerated during such a brief interval. The last water stop is repeated in the chamber and the remainder of the prescribed decompression completed. This procedure was tested by the author during 76 working dives at simulated depths of 80 to 190 feet. The method was found to be satisfactory within the test limits.

The advantages of surface decompression are:

- 1) The diver can be removed at once to a warm, safe, reasonably comfortable decompression



chamber. 2) In the chamber the actual pressure depth at a given stop can be precisely controlled in contrast to the condition in the water in heavy seas where depth control may be difficult.

For a report presenting the theoretical basis for a calculation of decompression schedules for nitrogen-oxygen and helium-oxygen mixtures used in diving, a report by R. D. Workman (Calculation of decompression schedules for nitrogen-oxygen and helium-oxygen dives, Research Report 6-65, Project No. SF-001-06-05; Task No. 11514, Sub-task 5, 26 May 1965) should be consulted. This report appeared too late for inclusion in the citation list for the present Sourcebook. This report includes definition, theory of exponential saturation and de-saturation and theory of limiting values of excess saturation permitted at various ambient pressures with helium and oxygen. An attempt has been made to simplify the presentation of the calculation procedures to implement the theoretical method. The necessary tables and work sheets used in calculations are presented by the author and there are also sample calculations of dive schedules. This discussion describes and appraises other methods of calculation developed in recent years.

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### 3. HELIUM—OXYGEN ADMINISTRATION

The rationale for using helium-oxygen mixtures in diving has been given on page 295 of Volume I of this Sourcebook. On pages 170 and 171 of the second Volume, helium-oxygen administration has been further discussed. At present helium is the only "non-depressant" inert gas which is known to be fully practical as a substitute for nitrogen in breathing mixtures (1736). In 1956 the current record depth of diving with helium and oxygen was 561 feet (in a pressure tank) and 500 feet (in the open sea). Since then a dive has been made to 1000 feet with helium as one of the constituent inert gases. Helium provides an advantage for long, deep dives, since it reduces respiratory resistance; but

it is not known yet whether the elimination of carbon dioxide from the lungs is significantly interfered with by increasing the gas density at depth. Helium would therefore be helpful for this reason: if medullary depression by nitrogen is involved in the enhanced susceptibility to oxygen poisoning observed in the use of nitrogen-oxygen mixtures, the operational objectives of "mixed gas" diving may have to be sought with helium.

Helium-oxygen tables differ from the air tables in the following major respects: the partial pressure of the inert gas at depth and not the depth determines the use of the tables; the rate of ascent from the bottom to the first stop varies; the rate of ascent between stops varies; the time of ascent from one stop to the next is included in the time of the subsequent stops; and repetitive dives are not permitted (1740). There are oxygen limits in the helium-oxygen diving procedure: for exposure times up to 30 minutes 2.0 atmospheres oxygen is the limit, and the allowable oxygen percentage under 30 minutes may be determined by the following formula where  $D$  = depth: maximum oxygen percentage equals  $\frac{(2.0 \times 33)}{(D + 33)}$ . The main difference between air and helium-oxygen decompression methods is the use of partial pressure of inert gas instead of actual depth. The compression schedules are given for each 10 feet of partial pressure from 60 to 410 feet and for bottom times of 10 to 240 minutes. An emergency table for the procedure for the use of air instead of oxygen or a helium-oxygen mixture is given. In case oxygen poisoning occurs during helium-oxygen decompression and the diver is within five minutes of surface time; start ascent at once. After surfacing place the diver in a chamber immediately and proceed with surface decompression, doubling the missed time and adding it to the chamber stop, using oxygen in the chamber. When decompression is completed keep the diver close to the chamber and watch for symptoms. If prompt ascent is not possible, bring the diver up 10 feet at once, shift to helium-oxygen or air, put the diver on open circuit, use the emergency table decompression and bring up for surface decompression.



After the references in the present Volume of the Sourcebook had been tabulated, there was published *Helium-oxygen Decompression Tables and Procedures*, extract from *U.S. Navy Diving Manual* (NAVSHIPS 250-538), prepared by U.S. Naval School, Deep Sea Divers, U.S. Naval Weapons Plant, Washington 25, D.C., January 1962. This report was promulgated as an aid in the teaching of and familiarization with the standard Navy helium-oxygen partial pressure tables and as a convenient reference for use at diving stations. The material is extracted from the *U.S. Navy Diving Manual* as stated and includes changes which reflect alterations in technique. Formulas are provided for the computation of partial pressures of gases, for the effect of atmosphere, the maximum oxygen percentage and tables delineating oxygen partial pressure limits. There are tables describing the rate of ascent and the actual partial pressure tables.

In recent studies of helium exchange in diving, Duffner (1731) 1962, and Duffner, Snyder and Smith (1732) 1959, have employed a theoretical no-decompression curve for dives in which an 80 percent helium and 20 percent oxygen is employed. One hundred and nine test dives were then performed using depth-time combinations following along this curve using 17 enlisted Navy divers as subjects. The limiting rate of ascent was also investigated following dives in which an 80 percent helium-20 percent oxygen breathing mixture was used. Seventy-eight dives employing decompression stops were also carried out. The findings were as follows: 1) there is no greater risk of decompression sickness with a helium-oxygen mixture than there is with air during dives to depths of less than 200 feet and of less than 180 minutes duration; 2) the helium uptake can be described with precision and accuracy for the purpose of computing decompression tables by employing three power function equations; 3) rates of ascent as high as 75 feet per minute can be tolerated from 120 feet to the surface, and rates as high as 120 feet per minute can be tolerated from 120 feet to 30 feet. The authors concluded that: 1) the use of helium-oxygen mixtures is feasible in mixed-gas SCUBA diving; 2) the range of activity can be covered by using a 50 percent and a 70 percent helium

mixture; 3) a short and simple decompression procedure can be developed.

Since the references in the present volume of the Sourcebook have been compiled, there appeared by R. D. Workman and J. L. Reynolds the Research Report 1-65, *Adaptation of Helium-oxygen to Mixed Gas SCUBA*, Project No. F-011-06-01 Task 3361, Test 1, U.S. Navy, Experimental Diving Unit, Washington Navy Yard, Washington, D.C., 1 March 1965. The authors have developed a decompression procedure using helium-oxygen mixtures in mixed gas SCUBA to allow repetitive dives to a depth of 200 feet. This procedure employs modified Haldane principles. The repetitive diving procedure provides a system by which a diver can determine the necessary increase in decompression time on successive dives, based on the amount of excess inert gas tension in the body tissues after completion of previous dives. The amount of decompression required is decreased by the time interval at the surface between dives. The information required for the use of this system is obtained from four tables: 1) the decompression table, 2) the no-decompression dive table, 3) the surface interval credit table and 4) the repetitive dive time table. A method for the use of oxygen decompression at 30 and 20 feet water-stops is also provided. The validity of this procedure is based on tests of 486 dives in which 28 three-dive series and 68 oxygen decompression dives were made. The procedure as recorded is considered satisfactory and is recommended for further testing under operational conditions in the field before service-wide use.

For a case history illustrating decompression problems of diving to 600 feet, a report by Crocker and Hempleman (1730) 1957, should be consulted. These authors believe that postwar experience with helium diving tables, based on Haldane's principles, indicates that they are unreliable for any but the shortest dives between 360 and 500 feet, and that any dive deeper than 500 feet might produce bends. Consequently when the question of providing tables for a dive to 600 feet arose it seemed that if the same methods were used not only would there be a strong likelihood of bends, but they might well appear in the early stages of decompression while the diver was still in the surface decompression

chamber. This was too great a risk to take and it was therefore decided to adopt an entirely different approach to the problem. A new method of calculating decompression tables is described. Using this new method tables were worked out for dives at three depths: 300, 450 and 600 feet. The first part of the trial consisted of four dives to 300 feet. All four were completed without incident except for bends sustained by one of the surface decompression chamber attendants. The first attempt to carry out the 450 foot dive was unsuccessful because the diver exceeded the depth required by 36 feet. A further dive to 450 feet was successful in every respect. The 600 foot dive was carried out on 12 October 1956 in a Norwegian fjord from the *H.M.S. Reclaim*. The diver arrived on the bottom of the shot-rope after seven minutes and started his task of shackling wire onto a ring bolt. Two minutes later having had a reasonable time in which to complete his task, he was told to "stand by to come up," whereupon he attempted to pass a message which, due to the distortion of his voice over the telephone by the high pressure of the helium, was quite unintelligible to those on the surface. When after a further two minutes this message had not been received, he was hauled up to his first stop at 260 feet in accordance with the decompression schedule. An error was made in estimating the depth of the first stop; consequently the diver spent four minutes extra on helium at 250 feet. Subsequent decompression proceeded without incident until some six hours later when the surface decompression chamber was brought to atmospheric pressure from 30 feet. The diver developed pains in both shoulders which got worse as he was transferred to the main chamber with his attendant. They were both recompressed to 50 feet and when all symptoms were fully relieved he was therapeutically decompressed. It was concluded that useful work is possible at 600 feet, provided heavy muscular effort is not required. The risk of decompression sickness by any present method of calculation cannot be avoided and it is recommended that no further dives to these depths be performed until there is a method of transferring divers from the surface decompression chamber into the main chamber without bringing them back to atmospheric pressure. Unless such a

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#### 4. OXYGEN ADMINISTRATION

For a paper on the possible role of oxygen in the genesis of decompression sickness, a paper by Donald (1742) 1955, should be consulted. Rashbass and Eaton (1718) 1957, have also reported on the effect of oxygen concentration on the occurrence of decompression sickness. The experi-



ments carried out by these investigators indicates that the pressure of oxygen increases slightly the probability of bends and that a reasonable estimate of its contribution would be to consider it as nitrogen present in one-fourth to one-third of its concentration. Therefore air would have a tendency to produce bends as though it were some 86 percent nitrogen.

R. D. Workman has prepared a report entitled, "Oxygen decompression following air dives for use in hyperbaric oxygen therapy", Research Report 2-64, Project F-011-06-01, Task 3361, Test 7, 15 December 1964. This report appeared too late for inclusion in the citation list. In this study two decompression schedules with the use of oxygen were tested to provide three and four hour air exposures at 3 atmospheres absolute pressure, required for use in hyperbaric oxygen treatment. Schedules for such long exposures have not been available previously to allow use of oxygen breathing during decompression so that the decompression time can be shortened. Six subjects were exposed to air breathing in a dry pressure chamber at 70 feet equivalent depth in sea water for periods of 180 and 240 minutes respectively. Decompression was carried out with oxygen breathing at 30, 20 and 10 foot stops. All six subjects exposed for 180 minutes were symptom-free following decompression. Of six subjects exposed for 240 minutes, one subject developed transient vertigo one hour post dive, which resolved promptly with oxygen breathing at a depth of 60 feet. Greater than average susceptibility to decompression sickness from such prolonged exposures in this subject is considered to be a severe test of adequacy for this schedule. Thus the schedules

tested should provide efficient decompression for these prolonged exposures with minimal risk of symptoms of decompression sickness. No manifestations of oxygen toxicity appeared during the oxygen decompression periods. Risk of oxygen toxicity should be minimal with the use of these schedules since the exposure is well within the safe limits for subjects at rest. Figure 4 reproduces Table 1 of Workman's report and shows air exposure with oxygen decompression schedules for hyperbaric oxygen therapy.

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Figure 4

TABLE 1.—AIR EXPOSURE WITH OXYGEN DECOMPRESSION SCHEDULES FOR HYPERBARIC OXYGEN THERAPY

Depth (ft)	Exposure Time (min)	Time to First Stop (min)	Decompression Stops Breathing 100% Oxygen			Total Ascent Time	Repet. Group	
			(ft)	30	20			10
70	180	5		5*	20*	25*	58	Z
70	240	5		10*	25*	35*	78	Z

\* Ascent rate, between stops and surfacing is at 10 feet/minute.

## 5. RECOMPRESSION TREATMENT AND PROCEDURES

An essential source on recompression treatment of decompression sickness is that provided by E. H. Lanphier in Chapter 7, *Fundamentals of Hyperbaric Medicine*, Publication No. 1298, National Research Council, Washington, D.C., 1966. As Lanphier has pointed out, the purpose of recompression is to provide prompt and lasting relief of the signs and symptoms of decompression sickness and of air embolism. The procedure of recompression must be designed to reduce the bubbles to a size at which they become asymptomatic. Also the therapeutic objective is to ensure that no bubble again becomes symptomatic upon subsequent decompression. Finally, it is necessary to conduct the decompression phase in such a way that no new bubbles form in the process.

There are a number of important considerations in applying recompression treatment to problems of decompression sickness. It is highly important to give treatment even in doubtful cases. Failure to do so can be a serious error. It is also significant that recompression procedures be initiated at once and not delayed. The longer the delay the deeper the victim will have to be taken for the relief of symptoms. The divers should be kept near the chamber for at least 24 hours after recompression treatment in case there is a return of symptoms. It is to be noted that symptoms of bends may sometimes become temporarily worse if pressures are applied too quickly. Should this occur the compression should be arrested for the time being and the pressure then slowly raised at a rate which is tolerable to the diver. In all cases and especially in serious paralysis, the capacity of the diver to stand up and walk the length of the chamber should always be tested. This test should be routinely made before the diver leaves the depth of relief of symptoms, and also made at the completion of the 30 foot stops.

Figures 5 through 8 are reproduced from the U.S. Navy Diving Manual, BuShips (1728) 1959. Figure 5, which reproduces Table 1-20, outlines briefly the treatment of an unconscious diver. Figure 6 (Table 1-21) provides a treatment schedule for varying degrees of severity of decompression sickness and air embolism. The Figures 7 and 8 (Table 1-22) gives a compact

set of notes on recompression. As pointed out in this figure the most frequent errors related to treatment are the failure of the diver to report symptoms early, failure to treat doubtful cases, failure to treat promptly, failure to recognize serious symptoms, failure to treat adequately and finally failure to keep the patient near the chamber after treatment.

For an excellent paper on recompression treatment, the report by M. W. Goodman and R. D. Workman, *Minimal-recompression, oxygen-breathing approach to treatment of decompression sickness in divers and aviators*, BuShips Project SF 011 06 05, Task 11513-2 (Research Report 5-65), 15 November 1965, U.S. Navy Experimental Diving Unit, Washington Navy Yard, Washington, D.C. should be consulted. This report appeared subsequent to the preparation of the bibliographic lists for the current Volume of the Sourcebook. As these authors have pointed out, there is a growing awareness of the incremental frequency with which difficulties are encountered in recompression treatment of severely injured patients, and of the grossly inadequate decompressions now characterizing the civilian diver casualty population applying to Naval recompression facilities. For this latter reason evaluation and clinical trials of therapeutic procedures alternative to U.S. Navy treatment tables were carried out by the authors. These techniques are particularly suitable for recompression management of aviators dysbarism when descent to sea level has not provided complete relief. The proportion of good results obtained with initial recompression trials with these procedures has significantly exceeded that obtained in recent years with the Diving Manual tables, although the current series reported by the authors of 79 cases surpassed comparable casualty groups in average case severity. Hypothetical and practical aspects of the treatment concept and techniques are presented by the authors as well as contra-indications. There were no adverse responses to the 2.8 atmospheres absolute  $P_{O_2}$  and nine volunteer human subjects showed no impairment of timed vital capacity following test exposures. It was concluded that the current U.S. Navy recompression procedures are in general reliable therapeutic schedules for divers who have reported "bends with pain only" subsequent



to exposures conducted in accordance with procedures set forth by the U.S. Navy Diving Manual. Current U.S. Navy recompression procedures are generally speaking, inadequate in the management of severe decompression sickness following grossly inadequate decompressions from compressed air dives. The recompression treatment procedures reported by the authors have afforded complete, firm relief to divers stricken with severe decompression sickness. Efficacy has also been demonstrated in 14 cases which followed "saturation" dives and in three cases of altitude dysbarism. It was reported that 56 percent of 79 cases fulfilled the standard

criteria for mandatory application of U.S. Navy treatment tables. The incidence of unsatisfactory first-recompression results was 3.6 percent for the group managed within the limits of a "minimally-adequate" routine. Overall, there was an 8.9 percent failure incidence, and for the adequately-managed cases a 2.0 percent failure of the initial recompression trials. The authors recommend taking steps and seeking approval for promulgation of these treatment procedures in the next edition of the Diving Manual. They believe that current U.S. Navy treatment tables should be retained with the oxygen recompression procedures alternately

Figure 5

TABLE 1-20

### TREATMENT OF AN UNCONSCIOUS DIVER

(Loss of consciousness during or within 24 hours after a dive. See art. 1.6.4)

1. IF NOT BREATHING, *start manual artificial respiration at once.* (See tables 1-23, 1-24, and 1-25.)
2. RECOMPRESS PROMPTLY. (See note (d).)
3. Examine for injuries and other abnormalities; apply first aid and other measures as required. (Secure the help of a medical officer as soon as possible.)

#### NOTES

##### *Artificial respiration*

- (a) Shift to a mechanical resuscitator if one is available and working properly, but never wait for it. Always start a manual method first.
- (b) Continue artificial respiration by some method without interruption until normal breathing resumes or victim is pronounced dead. Continue on way to chamber and during recompression. (Do not use oxygen deeper than 60 feet in chamber.)

##### *Recompression*

- (c) Remember that an unconscious diver may have air embolism or serious decompression sickness even though some other accident *seems* to explain his condition.
- (d) Recompress unless—
  - (1) Victim regains consciousness and is free of nervous system symptoms before recompression can be started.
  - (2) Possibility of air embolism or decompression sickness can be ruled out without question.
  - (3) Another lifesaving measure is absolutely required and makes recompression impossible.
- (e) Try to reach a recompression chamber no matter how far it is.
- (f) Treat according to treatment TABLE 3 or 4 (see table 1-21), depending on response. Remember that early recovery under pressure never rules out the need for adequate treatment.

## GENERAL PRINCIPLES OF DIVING

TABLE 1-21. — *Treatment of decompression sickness and air embolism.*

Stops		Bends—Pain only				Serious symptoms	
Rate of descent—25 ft. per min.  Rate of ascent—1 minute between stops.		Pain relieved at depths less than 66 ft.  Use table 1-A if O <sub>2</sub> is not available.		Pain relieved at depths greater than 66 ft.  Use table 2-A if O <sub>2</sub> is not available.  If pain does not improve within 30 min. at 165 ft. the case is probably not bends. Decompress on table 2 or 2-A.		Serious symptoms include any one of the following:  1. Unconsciousness. 2. Convulsions. 3. Weakness or inability to use arms or legs. 4. Air embolism. 5. Any visual disturbances. 6. Dizziness. 7. Loss of speech or hearing. 8. Severe shortness of breath or chokes. 9. Bends occurring while still under pressure.	
						Symptoms relieved within 30 minutes at 165 ft.  Use table 3	Symptoms not relieved within 30 minutes at 165 ft.  Use table 4
Pounds	Feet	Table 1	Table 1-A	Table 2	Table 2-A	Table 3	Table 4
73.4	165	.....	.....	30 (air)	30 (air)	30 (air)	30 to 120 (air)
62.3	140	.....	.....	12 (air)	12 (air)	12 (air)	30 (air)
53.4	120	.....	.....	12 (air)	12 (air)	12 (air)	30 (air)
44.5	100	30 (air)	30 (air)	12 (air)	12 (air)	12 (air)	30 (air)
35.6	80	12 (air)	12 (air)	12 (air)	12 (air)	12 (air)	30 (air)
26.7	60	30 (O <sub>2</sub> )	30 (air)	30 (O <sub>2</sub> )	30 (air)	30 (O <sub>2</sub> ) or (air)	6 hrs. (air)
22.3	50	30 (O <sub>2</sub> )	30 (air)	30 (O <sub>2</sub> )	30 (air)	30 (O <sub>2</sub> ) or (air)	6 hrs. (air)
17.8	40	30 (O <sub>2</sub> )	30 (air)	30 (O <sub>2</sub> )	30 (air)	30 (O <sub>2</sub> ) or (air)	6 hrs. (air)
13.4	30	<div>↓ 5 (O<sub>2</sub>) ↓</div>	60 (air)	60 (O <sub>2</sub> )	2 hrs. (air)	12 hrs. (air)	First 11 hrs. (air) Then 1 hr. (O <sub>2</sub> ) or (air)
8.9	20		60 (air)	<div>↓ 5 (O<sub>2</sub>) ↓</div>	2 hrs. (air)	2 hrs. (air)	First 1 hr. (air) Then 1 hr. (O <sub>2</sub> ) or (air)
4.5	10		2 hrs. (air)		4 hrs. (air)	2 hrs. (air)	First 1 hr. (air) Then 1 hr. (O <sub>2</sub> ) or (air)
Surface			1 min. (air)			1 min. (air)	1 min. (air)

Time at all stops in minutes unless otherwise indicated.

Figure 6



U.S. NAVY DIVING MANUAL

TABLE 1-22

NOTES ON RECOMPRESSION	
Explanation: All references to TABLES indicate parts of table 1-21 "Treatment of Decompression Sickness and Air Embolism."	
<p>1. <i>General Considerations</i></p> <p>a. Follow TREATMENT TABLES (table 1-21) accurately.</p> <p>b. Permit no shortening or other alteration of tables except on advice of trained <i>diving medical officer</i> or in extreme emergency.</p>	<p>2) Complete the treatment according to TABLE 4.</p> <p>b. <i>Following treatment:</i></p> <p>1) Recompress to depth giving relief.</p> <p>2) If depth of relief is less than 30 feet,</p> <p>a) Take to 30 feet.</p> <p>b) Decompress from 30-foot stop according to TABLE 3.</p> <p>3) If relief occurs deeper than 30 feet,</p> <p>a) Keep patient at depth of relief for 30 minutes.</p> <p>b) Complete remaining stops of TABLE 3.</p> <p>NOTE.—If original treatment was on TABLE 3, use TABLE 4.</p> <p>4) Examine carefully to be sure no serious symptom is present. If the original treatment was on TABLE 1 or TABLE 2, appearance of a serious symptom requires full treatment on TABLE 3 or TABLE 4.</p>
<p>2. <i>Rate of Descent in Chamber</i></p> <p>a. Normal rate is 25 feet per minute.</p> <p>b. Serious symptoms: rapid descent is desirable.</p> <p>c. If pain increases on descent: stop, resume at a rate tolerated by patient.</p>	<p><b>MOST FREQUENT ERRORS RELATED TO TREATMENT</b></p> <ol style="list-style-type: none"> <li>1. Diver's failure to report symptoms early.</li> <li>2. Failure to treat doubtful cases.</li> <li>3. Failure to treat promptly.</li> <li>4. Failure to recognize serious symptoms.</li> <li>5. Failure to treat adequately.</li> <li>6. Failure to keep patient near chamber after treatment.</li> </ol>
<p>3. <i>Treatment Depth</i></p> <p>a. Go to full depth indicated by table required.</p> <p>b. Do not go beyond 165 feet except on decision of medical officer.</p>	
<p>4. <i>Examination of Patient</i> (see article 1.6.2(14))</p> <p>a. If no serious symptoms are evident and pain is not severe, examine thoroughly before treatment.</p> <p>b. If any serious symptom is noted, do not delay descent for examination or for determining depth of relief.</p> <p>c. In "pain only" cases where relief is reported before reaching 66 feet, make sure it is complete before deciding on TABLE 1.</p> <p>d. On reaching maximum depth of treatment, examine as completely as possible to detect</p> <ol style="list-style-type: none"> <li>1) Incomplete relief</li> <li>2) Any symptoms overlooked</li> </ol> <p>NOTE.—At the very least, have patient stand and walk length of chamber.</p> <p>e. Recheck before leaving bottom.</p> <p>f. Ask patient how he feels before and after coming to each stop and periodically during long stops.</p> <p>g. Do not let patient sleep through changes of depth or for more than an hour at a time at any stop. (Symptoms can develop or recur during sleep.)</p> <p>h. Recheck patient before leaving last stop.</p>	<p>ALWAYS KEEP DIVER CLOSE TO CHAMBER FOR AT LEAST 6 HOURS AFTER TREATMENT. (Keep him for 24 hours unless very prompt return can be assured.)</p>
<p>5. <i>Patient Getting Worse</i></p> <p>a. Never continue bringing a patient up if his condition is worsening.</p> <p>b. Treat as a <i>recurrence during treatment</i> (see 6).</p> <p>c. Consider use of helium-oxygen as breathing medium for patient (see 8).</p>	<p>7. <i>Use of Oxygen</i></p> <p>a. Use oxygen wherever permitted by tables unless</p> <ol style="list-style-type: none"> <li>1) Patient has not had oxygen tolerance test, or</li> <li>2) Is known to tolerate oxygen poorly.</li> </ol> <p>b. Be sure mask fits snugly.</p> <p>c. Take all precautions against fire (see table 1-29).</p> <p>d. Tend carefully, being alert for symptoms of oxygen poisoning such as</p> <ol style="list-style-type: none"> <li>1) Twitching</li> <li>2) Dizziness</li> <li>3) Nausea</li> <li>4) Blurring of vision</li> </ol> <p>e. Know what to do in event of convulsion. Have mouth-bit available.</p> <p>f. If symptoms appear, remove mask at once.</p> <p>g. If oxygen breathing must be interrupted—</p> <ol style="list-style-type: none"> <li>1) On TABLE 1, proceed on TABLE 1-A.</li> <li>2) On TABLE 2, proceed on TABLE 2-A</li> <li>3) On TABLE 3, continue on TABLE 3 using air.</li> </ol> <p>h. At medical officer's discretion, oxygen breathing may be resumed at 40-foot stop. If this is done, complete treatment as follows:</p> <ol style="list-style-type: none"> <li>1) Resuming from TABLE 1-A: breathe oxygen:                     <ul style="list-style-type: none"> <li>at 40 feet for 30 minutes</li> <li>at 30 feet for 1 hour</li> </ul> </li> <li>2) Resuming from TABLE 2-A: breathe oxygen:                     <ul style="list-style-type: none"> <li>at 40 feet for 30 minutes</li> <li>at 30 feet for 2 hours</li> </ul> </li> <li>3) In both cases, then surface in 5 minutes still breathing oxygen.</li> <li>4) Resuming from TABLE 3: breathe oxygen:                     <ul style="list-style-type: none"> <li>at 40 feet for 30 minutes</li> <li>at 30 feet for first hour</li> <li>(then finish treatment with air)</li> </ul> </li> </ol>
<p>6. <i>Recurrence of Symptoms</i></p> <p>a. <i>During treatment:</i></p> <ol style="list-style-type: none"> <li>1) Take patient to depth of relief (but never to less than 30 feet; and not deeper than 165 feet except on decision of medical officer).</li> </ol> <p>(If recurrence involves serious symptom not previously present, take patient to 165 feet.)</p>	

Figure 7

## GENERAL PRINCIPLES OF DIVING

TABLE 1-22.—Continued

NOTES ON RECOMPRESSION	
<i>Explanation: All references to TABLES indicate parts of table 1-21 "Treatment of Decompression Sickness and Air Embolism."—Continued</i>	
<p>8. <i>Use of Helium-Oxygen</i></p> <p>a. Helium-oxygen mixtures (ratio about 80:20) can be used <i>instead of air</i> (not in place of oxygen) in all types of treatment and at any depth.</p> <p>b. Use of helium-oxygen is especially desirable in any patient who</p> <ol style="list-style-type: none"> <li>1) Has serious symptoms that fail to clear within a short time at 165 feet.</li> <li>2) Has recurrence or otherwise becomes worse at any stage of treatment.</li> <li>3) Has any difficulty in breathing.</li> </ol>	<p>Rule 2. <i>Maximum interval between ventilations:</i></p> <p>a. Not using oxygen: Interval (min.) <math display="block">\frac{\text{Chamber (or lock) volume (cu. ft.)}}{\text{Basic vent. req. (cu. ft./min.) (from rule 1)}}</math></p> <p>b. Using oxygen: Interval (min.) <math display="block">\frac{\text{Chamber (or lock) vol. (cu. ft.)}}{\text{No. of men br. O}_2 \times 10}</math></p> <p>a. Timing of ventilation:</p> <ol style="list-style-type: none"> <li>1) Use any convenient interval shorter than maximum from rule 2.</li> <li>2) (Continuous steady-rate ventilation is also satisfactory.)</li> </ol> <p>b. Volume used at each ventilation:</p> <ol style="list-style-type: none"> <li>1) Multiply volume requirement (cu. ft./min.) from rule 1 by number of minutes since start of last ventilation.</li> </ol> <p>c. Use predetermined exhaust valve settings to obtain required volume of ventilation. (See article 1.6.21 (18), (b).)</p>
<p>9. <i>Tenders</i></p> <p>a. A qualified tender must be in chamber</p> <ol style="list-style-type: none"> <li>1) If patient has had any serious symptom.</li> <li>2) Whenever patient is breathing oxygen.</li> <li>3) When patient needs unusual observation or care for any reason.</li> </ol> <p>b. Tender must be alert for any change in patient, especially during oxygen breathing. (See 7, d-f.)</p> <p>c. <i>Tender must breathe oxygen</i> if he has been with patient throughout TABLE 1 or TABLE 2</p> <p>TABLE 1: Breathe oxygen— at 40 feet for 30 minutes</p> <p>TABLE 2: Breathe oxygen— at 30 feet for 1 hour</p> <p>d. Tender in chamber only through oxygen breathing part of TABLE 1 or 2 gains safety-factor by breathing oxygen for 30 minutes of last stop, but this is not essential. Tender may breathe oxygen during use of TABLE 3 or 4 at 40 feet or less.</p> <p>e. Anyone entering chamber and leaving before completion of treatment must be decompressed according to standard diving tables.</p> <p>f. Personnel outside must specify and control decompression of anyone leaving chamber and must review all decisions concerning treatment or decompression made by personnel (including medical officer) inside chamber.</p>	<p>11. <i>First Aid</i></p> <p>a. First aid measures may be required in addition to recompression. Do not neglect them.</p> <p>b. See table 1-26 and <i>Standard First Aid Training Course</i>, NAVPERS 1-0081.</p>
<p>10. <i>Ventilation of Chamber</i> (See art. 1.6.21, par. 18)</p> <p>Rule 1. <i>Volume of air required</i> (volume as measured at chamber pressure—applies at any depth):</p> <p>a. Basic requirement:</p> <ol style="list-style-type: none"> <li>1) Allow 2 cubic feet per minute per man.</li> <li>2) Add 2 cubic feet per minute for each man <i>not at rest</i> (as tender actively taking care of patient).</li> </ol> <p>b. When using oxygen: Allow 4 cubic feet of air <i>per man breathing oxygen</i> if this yields larger figure than basic requirement. (Do not add to basic requirement.)</p>	<p>12. <i>Recompression in the Water</i></p> <p>a. Recompression without a chamber is difficult and hazardous. Except in grave emergency, seek nearest chamber even if at considerable distance.</p> <p>b. If water recompression must be used and diver is conscious and able to care for himself:</p> <ol style="list-style-type: none"> <li>1) Use deep sea diving rig if available.</li> <li>2) Follow treatment tables as closely as possible.</li> <li>3) Maintain constant communication.</li> <li>4) Have standby diver ready.</li> </ol> <p>c. If diver is unconscious or incapacitated, send another diver with him to control his valves and otherwise assist him.</p> <p>d. If lightweight diving outfit or scuba must be used, keep at least one diver with patient at all times. Plan carefully for shifting rigs or cylinders. Have ample number of tenders topside and at intermediate depths.</p> <p>e. If depth is inadequate for full treatment according to tables:</p> <ol style="list-style-type: none"> <li>1) Take patient to maximum available depth.</li> <li>2) Keep him there 30 minutes.</li> <li>3) Bring him up according to TABLE 3 if he can tolerate exposure. (If patient has been taken beyond 100 feet, do not use stops shorter than those of TABLE 2-A.)</li> </ol>

Figure 8



available, particularly for use with severely stricken divers who have had grossly inadequate decompression.

Figure 9 in the present Sourcebook reproduces Figure 1 of Goodman and Workman's monograph. This figure provides the depth and time limits for oxygen breathing in the treatment of decompression sickness.

Rivera (1757) 1963, has conducted an intense, thorough analysis of 935 cases of decompression sickness among divers. Rivera's paper is an essential resource for any investigation of the efficacy of various treatment procedures for decompression sickness. Reference may be made also to a report by Sebelien (1758) 1954, who pointed out that recompression treatment may be successful even if initiated more than 24 hours after the onset of the condition. A case is presented which demonstrates this conclusion.

Mackay (1754) 1963, has warned against unwarranted confidence in the dogmatic application of recompression tables. He feels that the treatment of decompression sickness needs revision and invites attention to the possible demoralizing effect on patients and attendants of the chamber environment. The whole process of recompression can be very exhausting since there are inadequate provisions for restful sleep, and part of the arrangements are lacking in comfort, etc.

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1761. U.S. Navy. Treatment of diving accidents and diseases. pp. 97-108 in: *Curriculum for submarine medical officers (Diving medicine)*. U.S. Navy, BuPers, Washington, D.C., *NAVPERS 92427*, February 1957, 167 pp.

1762. Wittenborn, A. F. An analytical development of a decompression computer. pp. 82-91 in: *Second symposium on underwater physiology*. Edited by C. J. Lambertsen and L. J. Greenbaum, Jr. National Research Council, Washington, D.C. *N.R.C. Publication 1181*, 1963, 296 pp.

## 6. PRESELECTION TESTS

Physical standards for diving duty were published (1769) in 1956. The following areas are listed with limits for each: 1) history of disease, 2) age, 3) weight, 4) vision, 5) color vision, 6) teeth, 7) ears, 8) nose and throat, 9) respiratory system, 10) cardiovascular system, 11) gastrointestinal system, 12) genitourinary system, 13) skin, 14) temperament, 15) ability to equalize pressure and 16) sensitivity to oxygen. Candidates for diving training must be able to tolerate pure oxygen at a simulated depth of 60 feet for 30 minutes at rest. They must also be able to equalize pressure down to 50 pounds. Any of the following diseases in the history shall be disqualifying: 1) tuberculosis, asthma or chronic pulmonary disease; 2) chronic or recurrent sinusitis, otitis media or otitis externa; 3) chronic or recurrent orthopedic pathology; 4) chronic or recurrent gastrointestinal disorders; 5) chronic alcoholism. No candidate shall be accepted with a history of syphilis unless there has been adequate treatment and no signs of activity or organic involvement. Candidates beyond the age of 30 years shall not be considered for initial training in diving (the most favorable age being from 20 to 30 years). All divers upon reaching the age of 40 shall be examined in accordance with sub-article 15-30 (3) MMD. Diving candidates should be rugged individuals without a tendency towards overweight. Fat absorbs about five times the volume of nitrogen as does lean tissue, and because of the low circulatory rate of fatty tis-

FIGURE 1

## MINIMAL-PRESSURE, OXYGEN RECOMPRESSION TREATMENT OF DECOMPRESSION SICKNESS

METHOD USED WHEN RELIEF OF SYMPTOMS IS COMPLETE WITHIN 10 MINUTES AT 60 FEET				<p>COMMENCE O<sub>2</sub> BREATHING PRIOR TO DESCENT. DEPTH-TIME SCHEDULES SHOULD BE FOLLOWED WITH CARE.</p> <p>COMPRESSION: RAPID DESCENT IS DESIRABLE, BUT DO NOT EXCEED RATE TOLERATED BY PATIENT. DESCENT TIME, USUALLY 1-2 MINUTES, IS NOT COUNTED AS TIME AT 60 FEET. DO NOT HALT THE DESCENT TO VERIFY A REPORT OF SYMPTOM RELIEF.</p> <p>DECOMPRESSION: ASCENTS ARE CONTINUOUS AT UNIFORM 1 F.P.M. DO NOT COMPENSATE FOR SLOWING OF THE RATE BY SUBSEQUENT ACCELERATION. DO COMPENSATE IF THE RATE IS EXCEEDED. IF NECESSARY, HALT ASCENT AND HOLD DEPTH WHILE VENTILATING THE CHAMBER.</p> <p>INSIDE TENDER: TENDER ROUTINELY BREATHES CHAMBER AIR. IF TREATMENT SCHEDULE IS LENGTHENED (SEE BELOW), OR IF THE TREATMENT CONSTITUTES A REPETITIVE DIVE FOR THE TENDER, HE MUST BREATHE O<sub>2</sub> FOR THE FINAL 30 MINUTES, FROM 30 FEET TO THE SURFACE.</p>
DEPTH (FEET)	TIME (MINUTES)	BREATHING MEDIA	TOTAL ELAPSED TIME (MIN.)	
60	20	O <sub>2</sub>	20	<p>RELIEF OF SYMPTOMS: IF COMPLETENESS OF RELIEF IS AT ALL DOUBTFUL AFTER 10 MINUTES O<sub>2</sub> BREATHING AT 60 FEET USE THE 285 MINUTE SCHEDULE.</p> <p>IF SYMPTOMS RECUR, FRESH SYMPTOMS APPEAR, OR THE PATIENT'S CONDITION WORSENS, RETURN TO 60 FEET AND USE THE 285 MINUTE METHOD. IF RELIEF IS NOT COMPLETE AT 60 FEET, PROCEED WITH THE 285 MINUTE SCHEDULE, OBSERVING CLOSELY FOR ANY CHANGES OF THE PATIENT'S CONDITION, OR LENGTHEN THE SCHEDULE (SEE BELOW), OR RE-COMPRESS TO 165 FEET AND COMMIT THE PATIENT TO U.S.N. TREATMENT TABLE 2A, OR TABLE 4 IF SYMPTOMS ARE NOT RELIEVED WITHIN 30 MINUTES.</p> <p>A MEDICAL OFFICER QUALIFIED IN DIVING, OR THE DIVING SUPERVISOR (DIVING OFFICER; MASTER DIVER) CAN EXTEND THE 285 MINUTE SCHEDULE WITH A FOURTH O<sub>2</sub>-AIR SEQUENCE (20 MINUTES O<sub>2</sub>-5 MINUTES AIR) AT 60 FEET, OR A THIRD AIR-O<sub>2</sub> SEQUENCE (15 MINUTES AIR-60 MINUTES O<sub>2</sub>) AT 30 FEET, OR BOTH.</p>
60	5	AIR	25	
60	20	O <sub>2</sub>	45	
60-30	30	O <sub>2</sub>	75	
30	5	AIR	80	
30	20	O <sub>2</sub>	100	
30	5	AIR	105	
30-0	30	O <sub>2</sub>	135	
METHOD USED WHEN RELIEF OF SYMPTOMS IS NOT COMPLETE WITHIN 10 MINUTES AT 60 FEET				<p>RELIEF OF SYMPTOMS: IF COMPLETENESS OF RELIEF IS AT ALL DOUBTFUL AFTER 10 MINUTES O<sub>2</sub> BREATHING AT 60 FEET USE THE 285 MINUTE SCHEDULE.</p> <p>IF SYMPTOMS RECUR, FRESH SYMPTOMS APPEAR, OR THE PATIENT'S CONDITION WORSENS, RETURN TO 60 FEET AND USE THE 285 MINUTE METHOD. IF RELIEF IS NOT COMPLETE AT 60 FEET, PROCEED WITH THE 285 MINUTE SCHEDULE, OBSERVING CLOSELY FOR ANY CHANGES OF THE PATIENT'S CONDITION, OR LENGTHEN THE SCHEDULE (SEE BELOW), OR RE-COMPRESS TO 165 FEET AND COMMIT THE PATIENT TO U.S.N. TREATMENT TABLE 2A, OR TABLE 4 IF SYMPTOMS ARE NOT RELIEVED WITHIN 30 MINUTES.</p> <p>A MEDICAL OFFICER QUALIFIED IN DIVING, OR THE DIVING SUPERVISOR (DIVING OFFICER; MASTER DIVER) CAN EXTEND THE 285 MINUTE SCHEDULE WITH A FOURTH O<sub>2</sub>-AIR SEQUENCE (20 MINUTES O<sub>2</sub>-5 MINUTES AIR) AT 60 FEET, OR A THIRD AIR-O<sub>2</sub> SEQUENCE (15 MINUTES AIR-60 MINUTES O<sub>2</sub>) AT 30 FEET, OR BOTH.</p>
60	20	O <sub>2</sub>	20	
60	5	AIR	25	
60	20	O <sub>2</sub>	45	
60	5	AIR	50	
60	20	O <sub>2</sub>	70	
60	5	AIR	75	
60-30	30	O <sub>2</sub>	105	
30	15	AIR	120	
30	60	O <sub>2</sub>	180	
30	15	AIR	195	
30	60	O <sub>2</sub>	255	
30-0	30	O <sub>2</sub>	285	

Figure 9



sues the nitrogen may be eliminated from fatty tissue very slowly. This acts to increase the possible incidence of bends. The candidate should in general have no greater than a ten percent variation from the standard age-weight-height tables. For further physical requirements reference should be made to the U.S. Navy Diving Manual (1769).

Special reference may be made, however, to the matter of temperament. The special feature of diving duties necessitates a careful examination and assessment of the candidate's emotional, temperamental and intellectual soundness. Past or recurrent symptoms of neuropsychiatric disorder or of an organic disease of the nervous system are disqualifying. History of any form of epilepsy, or head injury with sequelae, or personality disorder also lead to disqualification. Neurotic tendencies, emotional immaturity or instability and asocial traits of a sufficient degree to militate against satisfactory adjustment shall all be disqualifying. Stammering or other speech impediment which might become manifest under excitement is also disqualifying. Intelligence should be within the normal range.

Constitutional factors that may be operating in decompression sickness have been studied by Wise (1770) 1963. In this study 589 divers who had never experienced symptoms of decompression sickness were compared with 414 treated cases of the same to determine if there were any difference of sufficient magnitude to be used as selection criteria. Among the factors explored (age, weight, height and body type) no useful differences between the groups could be found. A second problem was to determine whether the depth of the dive and body type interacted to influence the probability of contracting bends. These results suggested that the role of adipose tissue in the etiology of decompression sickness is not as great as has been thought.

A chapter on the selection and training of operational personnel by G. F. Bond has appeared in *Fundamentals of Hyperbaric Medicine*, Publication No. 1298, National Academy of Sciences, National Research Council, Washington, D.C., 1966 (chapter 14) pp. 144-148. This chapter should be perused, even though it does not discuss divers, since it does outline psychological

and physical requirements for chamber personnel that are somewhat similar, although perhaps not so rigorous. In discussing psychological requirements, Bond asserts that it is generally believed that claustrophobic tendencies in overt reactions constitute the sole psychological criterion for work in hyperbaric chambers. This is not exactly the case. Although both frank and latent claustrophobia are believed to be significant factors in personnel selection, it should also be noted that motivation, maturity and interpersonal compatibility merit equal consideration. Motivation is extremely important since the working conditions are relatively harsh with long periods of boring inactivity and frustrating physical restraints. The professional personnel have not quite the problems with motivation that may be found in the paramedical personnel of lower echelons. Since the crowded conditions of the chamber for relatively long periods of time bring personnel in close contact, it is essential that all team personnel have unusual maturity and compatibility. For further discussion of the physical requirements, Bond's chapter should be consulted.

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1764. Davies, W. The medical examination of underwater swimmers. *Practitioner*, 1961, 187: 783-786.

1765. Jullien, G. Etude des réactions pathologiques consécutives à la plongée sous-marine et au travail dans l'air comprimé. *Arch. Mal. prof.*, 1956, 17: 288-236.

1766. Parker, G. W. and R. S. Stonehill. Further considerations of the roentgenologic evaluation of flying personnel at simulated altitude. *Aerospace Med.*, 1961, 32: 501-504.

1767. Parsons, V. A brief review of aviator's decompression sickness and the high altitude selection test. *J.R. nav. med. Serv.*, 1958, 44: 2-13.

1768. Snyder, J. F. and G. J. Duffner. A methodological test of resistance of divers to decompression sickness. U.S. Navy. EDU, Naval Weapons Plant, Washington, D.C. *Project NS 185-005, sub task no. 5, test no. 10*, 13 November 1958, 12 pp.

1769. U.S. Navy. Physical standards for diving duty. pp. 6-8 in: *Submarine medicine practice*. U.S. Navy, BuMed. *NAVMED - P 5054*, Gov't. Printing Office, Washington, D.C. 1956, 357 pp.

1770. Wise, D. A. Constitutional factors in decompression sickness. U.S. Navy. EDU, Naval Station, Washington, D.C. *Research Rept. 2-63*, 26 April 1963, 18 pp.

## 7. DRUGS AND HYPOTHERMIA IN THE TREATMENT OF DECOMPRESSION SICKNESS

The use of drugs and/or hypothermia are not considered adequate substitutes for recompression in treatment of decompression sickness, however, they may be of adjunctive value.

Barthélème (1772) 1963, found in experiments on mice, rats and rabbits that coagulation time was altered during rapid decompression. There was hypercoagulability in dives to 30 meters and hypocoagulability at 60 meters. Since the use in rabbits of 5 mg. of heparin did not adversely affect (and sometimes improved) the condition of the animals, human therapy was tried. In five accidents—four decompression sickness and one air embolism—heparin was given (50–100 mgm. two times per day). The substance never aggravated the condition but usually caused improvement. Studies on the action of heparin in the treatment of decompression accidents have also been carried out by Laborit, Barthélème and Perrimon-Touchet (1776) 1961. Rabbits were pressurized to 5 Kg./cm.<sup>2</sup> for one hour with four minutes decompression. There were symptoms of bends including paraplegia, monoplegia, quadriplegia, dyspnea and pain. A control group of animals was also adequately decompressed to avoid bends. Heparin was given in the following doses: 7.5 mg./Kg. and 5 mg./Kg. No difference was noted for the two dose levels. Heparin was given when the symptoms appeared and then recompression was carried out. Some rabbits were given heparin without recompression; even then survival was greater than in non-recompressed, non-heparinized animals. The authors believe that heparin may be of benefit because of its vasodilator effect: the hyperemia reducing tissue damage resulting from anoxia.

The reader may refer also to a paper by Frada (1774) 1952, in which it is suggested that nicotinic acid may be of value in the treatment of patients with decompression sickness. The rationale for its use under these circumstances is not given.

In studies reported by Erde (1773) 1963, seven civilian divers with decompression sickness and central nervous system symptoms were treated with chamber recompression and some with re-

compression plus hypothermia. Most of the dives had been multiple dives with no stage decompression. No diver used a depth gauge, lead line or wrist watch. The time which elapsed between symptom manifestation and treatment ranged from 180 to 300 minutes. Most of the divers had cord lesions ranging from the ninth thoracic to the second lumbar levels. Bladder and bowel functions were impaired in all but two divers. Residual motor weakness was seen in one or both lower extremities, but was less common in the patients treated with hypothermia plus recompression. Since part of the symptomatic picture is ascribed to persistent gas foci within the central nervous system, a part may also be due to edema in these tissues despite recompression. The patients given hypothermia plus recompression experienced relatively prompt relief even before decompression had been completed. This report includes complete case histories and course of treatment for each of these divers.

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1772. Barthelemy, L. Blood coagulation and chemistry during experimental dives and the treatment of diving accidents with heparin. pp. 46–56 in: *Second symposium on underwater physiology*. Edited by C. J. Lambertsen and L. J. Greenbaum, Jr. National Research Council, Washington, D.C. *N.R.C. Publication 1181*, 1963, 296 pp.

1773. Erde, A. Experience with moderate hypothermia in the treatment of nervous systems of decompression sickness. pp. 66–81 in: *Second symposium on underwater physiology*. Edited by C. J. Lambertsen and L. J. Greenbaum, Jr. National Research Council, Washington, D.C. *N.R.C. Publication 1181*, 1963, 296 pp.

1774. Frada, G. L'acido nicotinico endovena quale terapia di elezione degli accidenti embolici dei cassonisti. *Rif. med.*, 1952, 66: 791–794.

1775. Hartmann, H. Blutgerinnungsuntersuchungen nach Dekompression. *Int. Z. angew. Physiol.*, 1961, 18: 439–443.

1776. Laborit, H., L. Barthélème and R. Perrimon-Touchet. Action de l'héparine dans le traitement des accidents de décompression. *Rev. Agressol.*, 1961, 2: 229–235.

## IV. EXPLOSIVE DECOMPRESSION

### A. GENERAL STUDIES

Although explosive decompression is essentially an altitude problem, this section has been



included because some of the pathological phenomena in explosive decompression are related to and resemble those pulmonary lesions found in escape accidents. Some of the effects of explosive decompression on animals have been reported by Grandpierre, Grognot and Violette (1779) 1953. In this study unanesthetized cats and dogs and anesthetized dogs were explosively decompressed from 9,000 to 15,000 meters in 0.019 seconds using the double caisson technique. The unanesthetized animals presented no problems in comportment, equilibrium or hearing except that occasionally an older dog showed a light intra-auricular hemorrhage. Immediate autopsy showed rare, hemorrhagic pulmonary suffusions but the heart was normal and the gastrointestinal tract was intact. No apparent cerebral lesions were present grossly or microscopically. Anesthetized dogs constantly presented auditory hemorrhage with a paracentesis of the tympanum. There was thoracic dilatation followed by an inspiratory apnea of short duration. There was a sinus bradycardia but no electrocardiographic abnormality.

1777. Beliaev, N. P. O vzryvnoi dekompressii pri razgermetizatsii kabiny. [On explosive decompression during dehermetization of the cabin.] *Vo.-med. Zh.*, 1961, 5: 72-75.

1778. Brown, F. W., III and R. H. Lee. A biophysical analog for explosive decompression studies in animals. U.S. Navy. Mine Defense Laboratory, Panama City, Fla. *Med. Res. Rept.* 3, 1959, 10 pp.

1779. Grandpierre, R., P. Grognot and F. Violette. Some particular effects of explosive decompressions on animals. *J. Aviat. Med.*, 1953, 24: 20-22.

1780. Haber, F. and H. G. Clamann. Physics and engineering of rapid decompression. A. General theory of rapid decompression. USAF. School of Aviation Medicine, Randolph Field, Texas. *Project no. 21-1201-0008, Rept.* no. 3, August 1953, 29 pp.

1781. Hitchcock, F. A. Physiological and pathological effects of explosive decompression. *J. Aviat. Med.*, 1954, 25: 578-586.

1782. Holmstrom, F. M. G. Collapse during rapid decompression. *J. Aviat. Med.*, 1958, 29: 91-96.

1783. Kolder, H. Explosive Ueberdruckdekompression. *Arch. exp. Path. Pharmacol.*, 1954, 233: 486-492.

1784. Santa Maria, L. J., and H. R. Greider. Gaseous cavity formation in explosively decompressed animals. *J. Aviat. Med.*, 1957, 28: 303-308.

## B. HEART AND CIRCULATION

In experimental animals explosive decompression has been shown to cause a fall in systemic

arterial blood pressure as well as bradycardia. Increased intrathoracic pressure with distention of lungs, occurring when the rate of decompression of the chamber exceeds the rate at which the lungs could decompress, is considered to be the primary cause of the fall in arterial pressure. Reflexes from distended abdominal organs are believed to play a contributing part.

The effects of explosive decompression and subsequent exposure to 30 mm. Hg upon the hearts of dogs have been reported by Burch, Kempf, Vail, Frye and Hitchcock (1785) 1952. The explosive decompression of dogs followed by exposure to an ambient pressure of 30 mm. Hg results in gas in the thoracic cavity with dilatation of the thoracic cage and partial collapse of the lungs. According to the authors gas also forms inside the heart in less than two minutes following explosive decompression. This gas then expands causing cardiac dilatation. There is reflex slowing of the heart, mediated through the vagus. The effect on the right heart occurs first and is more pronounced than on the left. The authors believe that the damage to the myocardium is greater than could be accounted for on the basis of anoxia alone, and therefore they concluded that dilatation of the heart caused by expanding gases plays an important part in producing the effects observed. Hitchcock, Frye and Kempf (1786) 1952, found that in these animals the mean arterial blood pressure dropped within 15 seconds to a value of 60-70 mm. Hg. The pulse pressure decreased drastically. Usually there was no recovery from the condition until recompression. The authors' results indicate that following explosive decompression complete circulatory arrest usually occurs. In an effort to determine the time at which circulatory arrest supervened, ten dogs were explosively decompressed to 30 mm. Hg and immediately after decompression Diodrast was injected into the external jugular vein and angiograms made at intervals of two to seven seconds for 25 seconds or longer. The circulation through the right heart, pulmonary vessels, left heart and the aorta could be followed in this manner. Results showed that circulatory arrest occurred within 16 seconds in all dogs and within 10 seconds in 6 of the 10 animals. Eight of the dogs had gas in the heart within 10 seconds and in one other

gas was found in 16 seconds. The Diodrast usually went no further than the right heart, although occasionally it was seen in the pulmonary vein or in the aorta and its branches. These data indicate that usually circulatory arrest, which results from the formation of gas in the cardiovascular system, occurs within 16 seconds after explosive decompression to 30 mm. Hg. Records of arterial blood pressure, however, indicate that occasionally circulatory arrest does not occur until a minute or more after explosive decompression. In such cases the circulatory collapse is probably due to anoxia.

1785. Burch, B. H., J. P. Kempf, E. G. Vail, S. A. Frye and F. A. Hitchcock. Some effects of explosive decompression and subsequent exposure to 30 mm. Hg. upon the hearts of dogs. *J. Aviat. Med.*, 1952, 23: 159-167.

1786. Hitchcock, F. A., S. A. Frye and J. P. Kempf. Circulatory arrest in dogs following explosive decompression to 30 mm. Hg. *Fed. Proc.*, 1952, 11: 71.

1787. Rosbaum, D. A. and F. A. Hitchcock. The extent and probable cause of cardio-vascular changes due to explosive decompression. USAF. WADC, Wright-Patterson Air Force Base, Ohio. *WADC Tech. Rept. 53-191*, 153-167, December 1953, 228 pp.

1788. Vail, E. G. Forces produced in the thorax by explosive decompression. *Fed. Proc.*, 1952, 11: 165.

1789. Vail, E. G. and F. A. Hitchcock. The temperatures in the lungs and heart before and after explosive decompression. USAF. WADC, Wright-Patterson Air Force Base, Ohio. *WADC Tech. Rept. 53-191*, 168-182, December 1953, 228 pp.

### C. RESPIRATORY SYSTEM

The reader is referred to pages 178 and to 180 of Volume II of this Sourcebook for a still current account of the effects of explosive decompression upon pulmonary function and pathology. The respiratory and pulmonary effects depend upon how drastic the explosive changes are. A paper by Pryor and Marks (1772) 1954, may be cited. The study in question was done to show the effects of repeated exposure to rapid and explosive decompression, the latter defined as decompression of aircraft pressurized at 8,000 feet in less than one second to 25,000 feet. In this case gas in the respiratory tree cannot be expelled quickly enough to accommodate the increased volume. In the authors' studies eight normal men from 23 to 42 years of age in good health had experienced 30 rapid decompressions from 8,000 to 25,000 feet within a period of one to two-and-a-

half seconds and explosive decompression (within a second) at least five or six times. All had engaged in positive pressure breathing (50-150 mm. Hg) which is also considered a potential insult to pulmonary tissue. In these subjects no evidence of altered pulmonary function could be found by any conventional ventilatory studies. It was found that total lung capacity, maximum breathing capacity, ratio of residual capacity to total capacity, index of pulmonary mixing and timed vital capacity were all within normal limits.

1790. Luft, U. C. and R. W. Bancroft. Transthoracic pressure in man during rapid decompression. USAF. Randolph Field, Texas. School of aviation medicine. *Rept. no. 56-61*, August 1956, 13 pp.

1791. Porton, W. M. Thoracale drukverschijnselen bij "explosive decompression." [Thoracic pressure symptoms in explosive decompression.] *Ned. Milit. Geneesk. T.*, 1957, 10: 264-274.

1792. Pryor, W. W. and G. Marks. Evaluation of pulmonary function after rapid or explosive decompression. *J. Amer. med. Ass.*, 1954, 1956: 1233-1235.

1793. Schilling, J. A. and R. B. Harvey. Effect of simulated altitude and explosive decompression on dogs with bilateral partial pulmonary resection. *Fed. Proc.*, 1954, 13: 129.

1794. Vail, E. G. Forces produced in the thorax by explosive decompression. *J. Aviat. Med.*, 1952, 23: 577-583.

### D. GASTROINTESTINAL SYSTEM

Vail, Rosenbaum and Hitchcock (1795) 1953, carried out roentgenographic studies on the effects of explosive decompression and exposure to an ambient pressure of 30 mm. Hg upon the gastrointestinal tract and upon the gall bladder of dogs. These animals exhibited massive dilatation of the stomach and intestine resulting from expansion of contained gases. The pressure produced in the stomach was found to be sufficient at times to cause regurgitation of stomach contents into the esophagus and mouth. On recompression this material might be aspirated into the lungs. There was no swelling or gas formation in the gall bladder.

1795. Vail, E. G., D. A. Rosenbaum and F. A. Hitchcock. Roentgenogram studies of the effects of explosive decompression and exposure to an ambient pressure of 30 mm. Hg. upon the gastro-intestinal tract and the gall bladder. USAF. WADC, Wright-Patterson Air Force Base, Ohio. *WADC Tech. Rept. 53-191*, 111-118, December 1953, 228 pp.



### E. LETHAL FACTORS AND PATHOLOGICAL LESIONS

Pulmonary hemorrhage is observed in animals exposed suddenly to pressure equivalents of 50,000 and 80,000 feet. Previous experiments have shown that no pulmonary lesions are found in animals decompressed to simulated altitudes below 35,000 feet. The left lung shows less extensive trauma than does the right, and in both lungs the apical poles, the posterior surfaces, and the thin pulmonary margins appear to be the most vulnerable areas. It has been considered that anoxic anoxia is of major importance as a causative factor in death resulting from explosive decompression injury in animals compressed to an altitude equivalent of 80,000 feet. It has been found that explosive decompression of rats to normal atmospheric pressure after exposure to positive pressures of 2-20 atmospheres for varying intervals of time shows effects depending upon the severity of the pressure change. Decompression from two to as much as six atmospheres is well tolerated and such decompressions may be considered completely innocuous in the rat. Decompression after a 50 second exposure to 30 atmospheres is invariably fatal. On the other hand animals will survive this pressure change when the time under pressure is reduced to ten seconds. Some studies lead to the conclusion that sudden increases in pulmonary pressure introduced by explosive decompression are of primary etiological significance in producing lesions in animals.

The pathological effects of explosive decompression to 30 mm. Hg have been described by Cole, Chamberlain, Burch, Kempf and Hitchcock (1796) 1953. Eighteen dogs were explosively decompressed from 520 down to 30 mm. Hg in 0.035 seconds. Six were held at 30 mm. Hg for 2.5 minutes and then recompressed to ground level in one minute (series I). Twelve were recompressed immediately after explosive decompression, six in one minute (series II), and six at a rate of a free fall (seven minutes; series III). Two animals in series I, all six in series II and two in series III survived. The consistent pulmonary lesions observed in animals from all of these series were atelectasis, hemorrhage and emphysema. It was found that blood occluded the bronchi and bronchioles in areas

adjacent or proximal to atelectic areas giving rise to the suggestion that hemorrhage contributes to the maintenance of atelectasis. Hemorrhage was consistently found in the heart, intestines, stomach, liver, spleen, kidney and brain of dogs in all series. Cytological changes included rupture of the cell walls, extrusion of cytoplasm with liberation of nuclei. These changes were seen in hepatic and renal cells. There was transverse fragmentation of the myocardial fibers and hemorrhage as well as separation of myofibrils and extrusion of cytoplasm at points of rupture. These changes were observed in the heart of all 18 dogs. There was hemorrhage in the middle and inner ears in 17 of the 18 dogs. In all animals the tympanic membrane was intact after the experiment.

1796. Cole, C. R., D. M. Chamberlain, B. H. Burch, J. P. Kempf and F. A. Hitchcock. Pathological effects of explosive decompression to 30 mm. Hg. *J. appl. Physiol.*, 1953, 6: 96-104.

1797. Domenici, F. Lesioni da decompressione esplosiva. *Rass. Clin. Scient.*, 1955, 21: 139-141.

1798. Gell, C. F., W. M. Hall and F. K. Mostofi. Pathologic evaluation of explosive decompression to 65,000 feet. *J. Aviat. Med.*, 1958, 29: 15-26.

1799. Grognot, P. and R. Senelar. Etude expérimentale des lésions vasculaires lors de décompressions explosives chez le chien. *Méd. aéro.*, 1958, 13: 49-58.

1800. Grognot, P. A. and F. Violette. Lésions anatomo-pathologiques au niveau du cortex cérébral et du poumon de chiens soumis à une décompression explosive (9.000 à 15.000 m). *Méd. aéro.*, 1952, 7: 476-480.

1801. Kolder, H. Explosive Dekompression auf Unterdruck: Die Folgen der Abnahme des Luftdruckes in kürzester Zeit. *S.B. öst. Akad. Wiss. Wien*, 1956, 165: 357-419.

1802. Kolder, H. Echte explosive Dekompression. *Int. Z. angew. Physiol.*, 1956, 16: 212-216.

1803. Kolder, H. and L. Stockinger. Feinstrukturelle Veränderungen in der Lunge nach explosiver Dekompression und Kompression. *Arch. exp. Path. Pharmacol.*, 1957, 231: 23-33.

1804. Lalli, G. and G. Paolucci. Pyruvic and glutamic oxalacetic transaminases of the serum of rabbits subjected to explosive decompression, in relation to the anatomical damage. *Panminerva med.*, 1959, 1: 338-341.

### F. TOLERANCE

Close and Ireland (1806) 1961, have stated that surgical alterations in airway resistance in albino rats and the administration of certain drugs to albino rats and guinea pigs may alter tolerance and lung pathology upon exposure to explosive decompression. Procedures which lower

airway resistance decreased damage and improved tolerance, while procedures which raise airway resistance increased damage and worsened tolerance. Administration of nor-epinephrine, which raises blood pressure, decreases the tolerance to explosive decompression. Perivascular hemorrhages of the larger lung vessels were observed in all fatal decompressions. In death resulting from lethal doses of nor-epinephrine there are exhibited histopathological changes which are remarkably similar to those seen in explosive decompression. Explosive decompression in the guinea pig in conjunction with hypoxic hypoxia or the administration of histamine produces striking hemorrhagic consolidation in the lungs at the capillary level which is atypical of uncomplicated explosive decompression damage. Increased capillary permeability is probably involved. On the basis of this and other pertinent facts the authors hypothesize that major damage in severe uncomplicated explosive decompression is possibly due to stretching of the pulmonary blood vessels in conjunction with increased pressure without resulting in their rupture. This finding is consistent with the pathological changes reported in certain lung traumata in man. Efforts to protect human subjects from the damaging effects of explosive decompression in the form of a partial pressure altitude suit have been reported by Hull (1808) 1952. The reader is referred to this study.

1805. Close, P. Tolerance to explosive decompression of albino rats in a 'fetal' posture. *J. appl. Physiol.*, 1960, 15: 589-591.

1806. Close, P. and R. Ireland. Effect of certain variations in the physiologic state on tolerance to explosive decompression. *Aerospace Med.*, 1961, 32: 1050-1060.

1807. Hartmann, H. Tierexperimentelle Dekompressionsversuch. *Int. Z. angew. Physiol.*, 1961, 18: 435-438.

1808. Hell, W. E. Explosive decompression protection. USAF. WADC. Wright-Patterson Air Force Base, Ohio. *Tech. note WCRD 52-63*, September 1952.

1809. Kolder, H. Die Abhängigkeit der Wirkung einer explosiven Dekompression vom absoluten Druck. *Pflüg. Arch. ges. Physiol.*, 1957, 264: 456-459.

1810. Kolder, H. Explosive Dekompression im Bereich oberhalb 1 Atmosphäre. *Int. Z. angew. Physiol.*, 1958, 17: 120-124.

1811. Malette, W. G., J. B. Fitzgerald and B. Eisenman. Rapid decompression. A protective substance. USAF. Aerospace medical center (ATC) School of Aviation Medicine, Brooks Air Force Base, Texas. *Rept. no. 60-62*, June 1960.

1812. Stickney, J. C. and D. W. Northup. Rat LD<sub>50</sub> in explosive decompression. *Amer. J. Physiol.*, 1953, 172: 347-350.

## V. EXPLOSIVE COMPRESSION

Two papers are included in this section dealing with rapid compression from one atmosphere to high pressures.

1813. Kolder, H. and F. X. Wohlzogen. Explosive Kompression im Bereich oberhalb 1 Atmosphäre. *Pflüg. Arch. ges. Physiol.*, 1957, 265: 348-354.

1814. Richmond, D. R., M. B. Wetherbe, R. V. Taborrelli, T. L. Chiffelle and C. S. White. hTe biologic response to overpressure. I. Effects on dogs of five to ten-second duration overpressures having various times of pressure rise. *J. Aviat. Med.*, 1957, 28: 447-460.

## VI. OXYGEN INTOXICATION

### A. EFFECTS OF INCREASED OXYGEN TENSION NOT IN EXCESS OF ONE ATMOSPHERE

#### 1. GENERAL STUDIES

For a review of the literature on oxygen intoxication the reader should consult the section on this subject in both the first and second Volumes of this Sourcebook. Since the references of the present volume were compiled and numbered, a new monograph has been published by the National Academy of Sciences, National Research Council (Publication No. 1298). This monograph entitled *Fundamentals of Hyperbaric Medicine* (1966) was prepared by the Committee on Hyperbaric Oxygenation of the National Research Council. This monograph should be freely used by the reader who is interested in oxygen toxicity.

The toxic effects of excess oxygen still remain a matter of considerable importance, and the mechanism of these toxic effects are not yet thoroughly understood. Exposure to oxygen concentrations above 60 percent of one atmosphere for sufficient time periods causes toxic effects both in animals and in human subjects, and the severity of these effects is in proportion to the concentration and to the duration of exposure. The severity also shows individual variations as well as variations from one species to another. Under such conditions oxygen has adverse effects upon the lungs, the blood and other tissues of the body, including also the central nervous system. For example, the administration of 100 percent oxygen to human beings continuously



for 24 hours at normal barometric pressure causes substernal distress in 86 percent of subjects. Breathing 75 percent oxygen causes symptoms in only 55 percent of subjects and breathing 50 percent oxygen leads to no symptoms. Administration of 100 percent oxygen for short periods, up to 12 hours, is probably safe, but when oxygen has to be given for periods beyond 12 hours it should be reduced to 60 percent unless this is insufficient to saturate the arterial blood. If 100 percent oxygen must be given it is mandatory that a careful check should be made of the symptoms most likely to occur as a result of high oxygen tension.

Papers by Scano (1823, 1824, 1825) 1958, comprise a review of oxygen effects. Reference should also be made to a report by Elbel, Ormond and Close (1815) 1961, on the effects of breathing oxygen before and after exercise. Athletes in better than average physical condition were given 100 percent oxygen during six minutes of rest, air during five minutes of treadmill running at eight miles per hour and oxygen during 19 minutes of recovery. The results were compared with a control procedure in which the same subjects breathed air throughout. It was found that the experimental procedures did not significantly facilitate recovery as based upon payment of oxygen debt, measured by a closed-circuit spirometric method. The experimental procedure depressed the pulse rate during the first two minutes of exercise and during the recovery period. It also caused the respiratory rate to increase at rest, to decrease during the initial part of the recovery and to increase during the latter part of the recovery. It increased the percentage of oxygen saturation of blood hemoglobin as measured by an ear oximeter during rest and during recovery. Lower oximeter readings were found during the latter part of the exercise period.

For a statement of the effects of oxygen inhalation upon normal man, a report by Lambertsen (1818) 1954, is recommended. The general effects of oxygen upon respiration are discussed, including increased respiratory minute volume which is followed by pulmonary irritation. There is increased sensitivity to normal chemical stimuli, for example carbon dioxide; there is also cerebral vasoconstriction with carbon dioxide accumulation. There is in addition a

decrease in reduced hemoglobin. The pulse rate is lowered as well as cardiac output, because of reduced heart rate and stroke volume. Cerebral vasoconstriction is apparently due to reduced  $P_{CO_2}$  from oxygen breathing and not due to a direct effect of oxygen upon the vessels.

1815. Elbel, E. R., D. Ormond and D. Close. Some effects of breathing oxygen before and after exercise. *J. appl. Physiol.*, 1961, 16: 48–52.

1816. Gell, C. F. Breathing oxygen. pp. 143–161 in: *Aerospace medicine*. Edited by H. G. Armstrong, Williams and Wilkins Co., Baltimore, 1961, 633 pp.

1817. Jongbloed, J. and H. van Goor. Zuurstof-toediening bij sport. [Administration of oxygen to sportsmen.] *Ned. Tijdschr. Geneesk.*, 1954, 98: 491–497.

1818. Lambertsen, C. J. Effects of oxygen inhalation upon normal man. pp. 55/9–55/12 in: *Pharmacology in medicine*. Edited by V. A. Drill, McGraw-Hill Book Co., Inc., New York, 1954, 1273 pp.

1819. Lambertsen, C. J. Physiological effects of oxygen. pp. 171–187 in: *Second symposium on underwater physiology*. Edited by C. J. Lambertsen and L. J. Greenbaum, Jr. National Research Council, Washington, D.C. *N.R.C. Publication 1181*, 1963, 296 pp.

1820. Mullinax, F. P., Jr. and D. E. Beischer. Oxygen toxicity in aviation medicine. *J. Aviat. Med.*, 1958, 29: 660–667.

1821. Orie, N. G. M., J. J. M. Vegter and W. Veeger. Zo genaamde zuurstofintoxicatie. [So-called oxygen poisoning.] *Ned. Tijdschr. Geneesk.*, 1953, 97: 733–741.

1822. Pugh, L. G. C. The effects of oxygen on acclimatized men at high altitude. *Proc. R. Soc. Med.* (Ser. B.), 1955, 143: 14–17.

1823. Scano, A. L'iperossia. *Riv. Med. aero.*, 1958, 21: 88–118.

1824. Scano, A. L'iperossia. *Riv. Med. aero.*, 1958, 21: 337–361.

1825. Scano, A. L'iperossia. *Riv. Med. aero.*, 1958, 21: 539–566, and 765–799.

## 2. EFFECTS ON THE SPECIAL SENSES

At atmospheric pressure oxygen may have adverse effects upon the visual system. Noell (1829) 1962, has stated that with hyperoxia the visual cell deteriorates leaving the ganglion and bipolar cells preserved. Continued exposure of the rabbit to oxygen at one atmosphere results in severe attenuation or disappearance of the electroretinogram with the b waves most susceptible. The electroretinogram (ERG) decline resembled an S-shaped survival curve with an average latency ranging from 20 minutes at 7 atmospheres to 100 minutes at 3 atmospheres. Recovery occurred unless exposure was extended for several hours beyond the occurrence of the first effect. The decline of the b wave is delayed if intra-

ocular pressure is continuously increased during exposure to four atmospheres, which results in decreased blood flow and provides a protection to about one-half an atmosphere. Adrenalectomy also afforded protection by causing a fall in tissue oxygen tension. High inspiratory carbon dioxide produced comparable ERG abnormality but required fifty percent concentration. The effect was not accumulative and recovery was rapid. If exposure is continued for five to eight hours beyond ERG changes, the damage is irreversible. Young rabbits are found to be more susceptible than adult animals. It may be mentioned parenthetically that in the adult man exposure to three atmospheres oxygen causes progressive failure of peripheral vision with maximal constriction at ten degrees and only temporary impairment of central vision.

Miller (1827) 1958, has studied the effect of breathing 100 percent oxygen upon the visual field and upon visual acuity recorded through the use of a tangent screen, a perimeter and a Clason acuity meter. A control study was made by having the subjects breathe air instead of the 100 percent oxygen during one test run. Each of the six subjects was examined with each of the three instruments before and after each hour of the test run. Analysis of the oxygen data and comparison of them with the air data revealed no significant depression or constriction of the central field and no sector defects; also the size of the blind spot remained essentially the same. A lack of significant alterations of the more peripheral isopters indicated no decreased sensitivity in this region. Central acuity was unchanged and peripheral acuity of the 100 percent oxygen test run at both five degrees and ten degrees did not differ significantly from that measured during the air-test run. The results indicated that vision tested in several regions from zero to 60 degrees suffers no apparent decrement as a result of the breathing of 100 percent oxygen at atmospheric pressure for a period of over four hours.

1826. Harris, J. G., D. E. Beischer and D. Eversen. The effects of inhalation of 100 per cent oxygen on performance of a task involving visual auditory conflict. U.S. Navy. NATB, School of Aviation Medicine, Pensacola, Fla. *Project no. MR005.13-1002, Sub task 11, Rept. no. 3*, 5 October 1960, 20 pp.

1827. Miller, E. F. Effect of breathing 100 per cent oxygen upon visual field and visual acuity. *J. Aviat. Med.*, 1958, 29: 598-602.

1828. Noell, W. K. Visual cell effects of high oxygen pressures. *Fed. Proc.*, 1955, 14: 107.

1829. Noell, W. K. Effects of high and low oxygen tension on the visual system. pp. 3-18 in: *Environmental effects on consciousness*. Edited by K. E. Schaefer, The MacMillan Company, New York, 1962, 146 pp.

### 3. EFFECTS ON THE CARDIOVASCULAR SYSTEM

The circulatory effects of oxygen at one atmosphere seem most likely to be caused by suppression of tonic activity of peripheral chemoreceptors. There is general agreement in the literature that at normal atmospheric pressure the breathing of 100 percent oxygen results in a slowing of the heart, a reduction of respiratory minute volume and a decrease in cardiac output. The slowing of the heart is considered to be almost entirely responsible for the reduction in cardiac output. Oxygen also produces changes in the circulation of regional vascular beds, thus there is constriction of coronary and cerebral vessels as the tension of oxygen is increased. This has also been observed in the eye as well as in the kidney. It is possible that these vasoconstrictor effects upon local circulation are due to the direct action of oxygen on the smooth muscle of blood vessels, and in addition to the possibility of these direct effects, central neurological and local chemical influences must be considered.

Bevan and Verity (1835) 1961, have presented an analysis of cardiovascular responses to short periods of inhalation of oxygen in cats anesthetized with chloralose. In these animals there was an immediate acute fall in arterial blood pressure accompanied by varying degrees of bradycardia. Following bilateral vagotomy the initial hypotension was still present. With inactivation of caroticoaortic chemoreceptor regions, no hypotension effect was seen, but small, slowly developing hypertension was observed originating peripherally. Barratt-Boyes and Wood (1834) 1958, found in normal healthy human subjects that administration of 95 percent oxygen at one atmosphere produced a fall in heart rate, with an increase in stroke volume but with no systemic change in cardiac output under the conditions of the experiment. Dressler, Slonim, Balchum, Bronfin and Ravin (1838) 1952, found a decrease in cardiac output during oxygen breathing. Re-



duced heart rate was also observed by Grandpierre, Tabusse and Bouverot (1839) 1955. Inhalation of pure oxygen at one atmosphere produced bradycardia in 18 cases out of 20, occasionally after 15 minutes, and always after an hour. Eighty percent and 60 percent mixtures produced comparable bradycardia, but a 40 percent mixture caused bradycardia in only 50 percent of the subjects tested. In the anesthetized dog bradycardia appeared less often, frequently being replaced by tachycardia, even during inhalation of pure oxygen, with the ECG changes being of the same category as those in man. The authors believe it possible to attribute bradycardia in certain cases, above all that produced at the very beginning of the inhalation of pure oxygen, to an action on the vaso-sensitive zones. Late appearance of bradycardia, when the blood has been superoxygenated for 15 minutes, does not appear to favor this mechanism in human beings. It was noted that most of the cardio-moderator reflexes were generally diminished in the course of the first hours following the inhalation of pure oxygen. Marshall, Swan, Burchell and Wood (1845) 1961, have studied the effect of breathing oxygen on pulmonary arterial pressure and on pulmonary vascular resistance in patients with ventricular septal defects. During cardiac catheterization pulmonary and systemic arterial blood pressure, arterial oxygen saturation, respiration and heart rate were continuously recorded during the change from breathing air to breathing 95–99.5 percent oxygen for 5–15 minutes in a series of 31 patients with ventricular septal defects. Pulmonary and systemic blood flows were also measured. Systemic arterial oxygen saturation began to increase about five seconds after the change from breathing air to breathing oxygen. Within a few seconds thereafter the pulmonary arterial pressure and heart rate began to decrease. These changes were complete within three minutes. Pulmonary blood flow increased on an average of 32 percent and systemic decreased by 15 percent. There was no consistent change in pulmonary arterial wedge pressure. The average calculated pulmonary resistance decreased by 36 percent and the systemic was increased. These changes were independent of pulmonary hypertension, of anesthesia and of the patient's age.

Oxygen may exert pathological effects upon the development of the vascular system, as has been shown by Allen (1830) 1961. Fertile white Leghorn eggs were exposed to 100 percent oxygen under very slight positive pressure during the first four days of incubation at 37–38°C. This exposure resulted in marked changes in the development of the vascular system. These were demonstrated by failure of development of the vitelline circulation, frequent massive hemorrhages in these areas and failure to develop an evident heart beat. These changes bear a remarkable similarity to the response seen in similar embryos exposed to various types of radiation. It is thus evident that such local concentrations of oxygen can inhibit the normal development of the vascular system. In a further study Allen (1831) 1963, demonstrated that there is a critical oxygen-nitrogen ratio for optimal development and maintenance of the vascular system of the chick embryo. Relevant studies by Gyllensten (1840) 1959, demonstrated that exposure of growing young mice to oxygen influences postnatal vascularization of the cerebral cortex. Thus continuous exposure to concentrations of oxygen (90–100 percent) for 5, 10, 15, 20 or 30 days caused a decrease in the relative vascularization of all laminae of the area striata.

As has been pointed out by Miles (1847) 1957, there is abundant evidence that breathing oxygen will lower the threshold for the occurrence of syncope, irrespective of its immediate cause, and therefore individuals breathing oxygen would be more likely to faint than when breathing air. To test this theory a simple experiment was devised that would bring a man breathing air to the brink of syncope. The test was carried out with 36 young adult men all experienced in the use of breathing apparatus. Each man was tested with air and with oxygen, one-half having air first and the remainder oxygen. All of the tests were done at the same time of day (late forenoon) and each man had a rest of 30 minutes between tests. Both air and oxygen were supplied from cylinders into a Douglas bag, no man knowing which he was breathing. The subject lay horizontally on a tilt table breathing with nose clip and mouthpiece from the bag for five minutes. This was followed by one minute of hyperventilation, on completion of which he was

tilted quickly to the upright position. Men were previously instructed in the routine and immediately on becoming upright took a final breath from the bag, exchanged the mouthpiece for a stout rubber pressure tube attached to a mercury manometer and blew hard against the pressure, with the object of maintaining as high a pressure as possible for as long as possible. The mercury pressure was recorded every ten seconds and the breath holding time noted. Throughout the test the subject was kept under observation and upon completion he was asked to give an account of his sensations. Of the 36 men three became unconscious on both air and oxygen and a further four on oxygen alone. Two had symptoms suggesting an approaching syncope on both air and oxygen but a further twelve had symptoms on oxygen alone. The order of performance of the tests did not influence the results and there was little difference between the mean pressures held on air and oxygen. The mean breath holding time was longer however, with oxygen. Less oxygen breathing can be shown to lower the threshold of syncope.

1830. Allen, S. C. Response of the developing vascular system of the chick embryo to hyperoxia. *Fed. Proc.*, 1961, 20: 421.

1831. Allen, S. C. The role of nitrogen in the problem of oxygen toxicity. *Fed. Proc.*, 1963, 22: 635.

1832. Arnould, P., J. Petit and M. Boulange. Effets ventilatoires de l'inhalation d'oxygène et d'azote purs par un poulmon vasculairement exclu, chez le Chien chloralosé. *C.R. Soc. Biol., Paris*, 1961, 155: 552-555.

1833. Barratt-Boyes, B. G. and E. H. Wood. Hemodynamic response of healthy subjects to exercise in the supine position while breathing oxygen. *J. appl. Physiol.*, 1957, 11: 129-135.

1834. Barratt-Boyes, B. G. and E. H. Wood. Cardiac output and related measurements and pressure values in the right heart and associated vessels, together with an analysis of the hemodynamic response to the inhalation of high oxygen mixtures in healthy subjects. *J. Lab. clin. Med.*, 1958, 51: 72-90.

1835. Bevan, J. A. and M. A. Verity. Cardiovascular response to oxygen inhalation in the anesthetized cat. *J. appl. Physiol.*, 1961, 16: 858-862.

1836. Cuypers, Y. and E. Evrard. L'influence de la circulation sur l'intoxication par l'oxygène. *Méd. aéro.*, 1957, 12: 59-67.

1837. Daly, W. J. and S. Bondurant. Effects of oxygen breathing on the heart rate, blood pressure, and cardiac index of normal men—resting, with active hyperemia, and after atropine. *J. clin. Invest.*, 1962, 41: 126-132.

1838. Dressler, S. H., N. B. Slonim, O. J. Balchum, G. J. Bronfin and A. Ravin. The effect of breathing 100% oxygen on the pulmonary arterial pressure in patients with pulmonary tuberculosis and mitral stenosis. *J. clin. Invest.*, 1952, 31: 807-814.

1839. Grandpierre, R., L. Tabusse and P. Bouverot. Modifications du rythme cardiaque provoquées par l'inhalation d'oxygène. *J. Physiol. Path. gén.*, 1955, 47: 185-190.

1840. Gyllensten, L. Influence of oxygen exposure on the postnata l vascularization of the cerebral cortex in mice. *Acta Morph. neerl. scand.*, 1959, 2: 289-310.

1841. Harris, A. S., R. W. Olsen, A. Estandía and T. J. Ford, Jr. Oxygen administration upon ventricular tachycardia and blood pressure in animals with acute myocardial infarction. *Circ. Res.*, 1953, 1: 83-86.

1842. Kilmore, M. A., R. M. Tomasello and H. F. Chase. Effect of PO<sub>2</sub> on cerebral blood flow. *Fed. Proc.*, 1964, 23: 206.

1843. Lundin, G. Nagra fysiologiska synpunkter pa syrgasbehandling. [Physiological aspects of oxygen therapy.] *Svenska Läkartidn.*, 1953, 50: 1082-1085.

1844. Manolescu, N., I. Pintilie, V. Teodorescu, M. Stoian, S. Schiau, L. Pascalov-Stoenescu, R. Stoenescu and G. Arsenescu. Cardiovascular changes in aviators during the oxygen pressure breathing test with the use of high altitude pressure suit. *Stud. Cercet. Fiziol.*, 1960, 5: 119-126.

1845. Marshall, H. W., H. J. C. Swan, H. B. Burchell and E. H. Wood. Effect of breathing oxygen on pulmonary artery pressure and pulmonary vascular resistance in patients with ventricular septal defect. *Circulation*, 1961, 23: 241-252.

1846. Meyer, J. S. and J. Hunter. Polarographic study of cortical blood flow in man. *J. Neurosurg.*, 1957, 14: 382-399.

1847. Miles, S. Oxygen syncope. *Gt. Brit. MRC, RNP, UPS. Rept. R.N.P. 57/880, U.P.S. 161*, January 1957, 5 pp.

1848. Morris, J. A., R. W. Smith, R. Beck and N. S. Assali. Oxygen effect on the isolated ductus arteriosus of the lamb. *Fed. Proc.*, 1963, 22: 343.

1849. Patterson, J. L., Jr., A. Heyman and T. Whatley. Cerebral circulation and metabolism in chronic pulmonary emphysema; with observations on the effects of inhalation of oxygen. *Amer. J. Med.*, 1952, 12: 382-387.

1850. Ratschow, M. Untersuchungen zur Wirkung des Sauerstoffgases in der Behandlung von Angiopathien. *Med. Klinik*, 1954, 49: 691-693.

1851. Ross, J., Jr., G. Kaiser and F. Klocke. Studies on the role of oxygen tension in the functional hyperemia of skeletal muscle. *Fed. Proc.*, 1964, 23: 207.

1852. Sayen, J. J., W. F. Sheldon, O. Horwitz, P. T. Kuo, G. Peirce, H. F. Zinzzer and J. Mead, Jr. Studies of coronary disease in the experimental animal. II. Polarographic determinations of local oxygen availability in the dog's left ventricle during coronary occlusion and pure oxygen breathing. *J. clin. Invest.*, 1951, 30: 932-940.

1853. Sharpey-Schafer, E. P. Syncope. *Brit. med. J.*, 1956, 1: 506-509.



1854. Smith, C. W., P. H. Lehan and J. J. Monks. Cardiopulmonary manifestations with high  $O_2$  tensions at atmospheric pressure. *J. appl. Physiol.*, 1963, 18: 849-853.

1855. Storstein, O. The effect of pure oxygen breathing on the circulation in anoxemia. *Acta med. scand.*, 1952, 269: (suppl.) 185 pp.

1856. Sugioka, K. and D. A. Davis. Hyperventilation with oxygen—a possible cause of cerebral hypoxia. *Anesthesiology*, 1960, 21: 135-143.

1857. Tabusse, L. Le seuil des perturbations organiques au cours de l'inhalation d' $O_2$  pur. *Méd. aéro.*, 1954, 9: 80-81.

1858. Womack, G. J. Evidence for the cerebral vasoconstrictor effects of breathing one hundred per cent oxygen. *Aerospace Med.*, 1961, 32: 328-332.

#### 4. EFFECTS ON BLOOD

In both animals and man exposure to high oxygen tension at ambient atmospheric pressure for prolonged periods of time results in reduction of erythropoietic activity. This has been confirmed by Cooperberg and Singer (1860) 1951, in guinea pigs, and by Gunther, Hodgson, Tohe and Quappe (1866) 1951, in rabbits. These investigators found that the plasma of anemic rabbits maintained free from contact with air produced a significantly larger reticulocyte response than that produced by injection of plasma of normal animals. These effects were produced in receptor rabbits. The plasma of anemic rabbits submitted to the action of oxygen produced a significantly smaller erythrocyte response in the injected animals than that produced by plasma maintained free from contact with the air. It is suggested by the authors that the action of oxygen on erythropoiesis is mediated through a humoral mechanism.

1859. Cole, R. B. and J. M. Bishop. Effect of varying inspired  $O_2$  tension on alveolar-arterial  $O_2$  tension difference in man. *J. appl. Physiol.*, 1963, 18: 1043-1048.

1960. Cooperberg, A. and K. Singer. The reaction of the bone marrow to high oxygen tension in normal and anemic guinea pigs. *J. Lab. clin. Med.*, 1951, 37: 936-947.

1861. Doll, E., K. König and H. Reindell. Das Verhalten der arteriellen Sauerstoffspannung und anderer arterieller blutgasanalytischer Daten in Ruhe und während körperlicher Belastung. *Pflüg. Arch. ges. Physiol.*, 1960, 271: 283-295.

1862. Fleisch, A. and P. C. Frei. De l'emploi de l'oxygène pur dans les oxygénateurs des coeurs-poumons artificiels. *Helv. physiol. acta*, 1960, 18: 464-466.

1863. Gibson, Q. H. The kinetics of reactions between haemoglobin and gases. *Prog. Biophys. biophys. Chem.*, 1959, 9: 1-53.

1864. Gibson, Q. H. and F. J. W. Roughton. The kinetics of dissociation of the first oxygen molecule from fully saturated oxyhaemoglobin in sheep blood solutions. *Proc. roy. Soc.*, 1955, 143: 310-342.

1865. Haab, P., J. Piiper and H. Rahn. Attempt to demonstrate the distribution component of the alveolar-arterial oxygen pressure difference. *J. appl. Physiol.*, 1960, 15: 235-240.

1866. Gunther, B., G. Hodgson, J. Tohe and O. Quappe. The inactivation by oxygen of the erythropoietic effect of plasma of rabbits rendered anemic by bleeding. *Acta physiol. lat. amer.*, 1951, 1: 271-276.

1867. Heller, M. L. and T. R. Watson, Jr. Arterial oxygenation during transition of 100 per cent oxygen to air breathing: polarographic  $Pa_{O_2}$  study. *Anesthesiology*, 1961, 22: 385-392.

1868. Hemmingsen, E. and P. F. Scholander. Specific transport of oxygen through hemoglobin solutions. Why is this transport abolished when opposed by a slight back pressure of oxygen? *Science*, 1960, 132: 1379-1381.

1869. Hitchcock, F. A., J. F. Atkinson and J. P. Kemph. Blood of dogs following controlled breathing of air and oxygen. *Fed. Proc.*, 1953, 12: 68.

1870. Ingvar, D. H., D. W. Lübbers and B. Siesjö. Measurement oxygen tension on the surface of the cerebral cortex of the cat during hyperoxia and hypoxia. *Acta physiol. scand.*, 1960, 48: 373-381.

1871. Lee, W. L., Jr., P. B. Caldwell, H. S. Schildkraut. Changes of lung volume, diffusion capacity, and blood gases in oxygen toxicity in humans. *Fed. Proc.*, 1963, 22: 395.

1872. Marx, T. I., W. E. Snyder, A. D. St. John and C. E. Moeller. Diffusion of oxygen into a film of whole blood. *J. appl. Physiol.*, 1960, 15: 1123-1129.

#### 5. EFFECTS ON LYMPH

Said, Davis and Banerjee (1873) 1964, have conducted a study on the  $P_{O_2}$  and  $P_{CO_2}$  of pulmonary lymph. Right thoracic duct lymph was sampled and simultaneously femoral arterial and right ventricular blood and alveolar gas sampled in six anesthetized dogs. During air breathing the  $P_{O_2}$  of lymph was slightly lower and the  $P_{CO_2}$  slightly higher than in arterial blood. On breathing 100 percent oxygen for up to five hours lymph  $P_{O_2}$  increased moderately but remained appreciably below arterial levels. Agreement between lymph and arterial blood  $P_{O_2}$  was restored with the induction of pulmonary edema; both fell to a similar level. The findings could be explained by 1) a dominant contribution to right duct lymph from the gas-exchange area of the lung normally or when pulmonary lymph flow was enhanced; and 2) by an admixture of hypoxic lymph from the non-respiratory part of the lung,

heart, pleural and peritoneal cavities. If lymph reflects tissue tensions, the alveoli may be the only tissue that normally operates at high oxygen tensions.

1873. Said, S. I., R. K. Davis and C. M. Banerjee.  $P_{O_2}$  and  $P_{CO_2}$  of pulmonary lymph. *Fed. Proc.*, 1964, 23: 469.

## 6. EFFECTS ON RESPIRATION

There is a lack of total agreement as to the precise effects upon respiration of oxygen or hyperoxygenated air at normal barometric pressures. However, it appears that oxygen administration does cause changes in breathing, although these may not be pronounced. Oxygen administration in animals reduces respiratory minute volume and this has also been observed in man.

There is a transient decrease in ventilation on administration of oxygen to normal persons at sea level, and this gives way within a short time to a light stimulation of respiration. Concurrently there is a decrease of the slope of the ventilatory response to carbon dioxide inhalation so that there may be both stimulation and depression. Bannister and Cunningham (1876) 1954, have shown that in all instances addition of oxygen to the inspired air increases the time required by athletic and non-athletic subjects to reach a breaking point when operating on a motor-driven treadmill. The performance was more improved by 66 percent and by 100 percent oxygen than by 33 percent. With 66 percent oxygen three of the subjects did not reach a breaking point within 23 minutes. The discomfort which they had experienced when breathing air was replaced by a feeling of positive well-being. In contrast when breathing 100 percent oxygen they never did feel elation and all reached a breaking point within 21 minutes. The depressant action of 100 percent oxygen when compared with 66 percent has been discussed by the authors. They tentatively suggest that it might be due to increases in the cerebral circulation resulting from the excess of circulating carbon dioxide and lactate. Such an increase would nullify the protection from the deleterious effects of high-pressure oxygen afforded to the brain by the cerebral vasoconstriction which occurs at rest when pure oxygen is breathed. Asmussen and Nielsen (1874) 1958, have studied

the regulation of respiration in heavy work in young normal subjects by measuring the arterial oxygen tensions and various respiratory functions in rest and in work when breathing atmospheric air and when breathing air mixtures with augmented or lowered oxygen concentrations. It was found that the arterial  $P_{O_2}$  in heavy work with pronounced hyperventilation (i.e. increased ventilation per liter oxygen uptake and decreased alveolar  $P_{CO_2}$ ) was of the same magnitude (87 mm. Hg, range 82–94 mm. Hg) as in rest and in light work (87 mm. Hg, range 79–96 mm. Hg). This value is lower than the reported threshold of  $P_{O_2}$  for the chemoreceptors in animals and humans. The breathing of 33 percent oxygen diminished the hyperventilation of heavy work and increased the arterial  $P_{O_2}$  to 183 mm. Hg (range 161–190 mm. Hg). This value is well above the reported threshold  $P_{O_2}$  for the chemoreceptors. Breathing of 100 percent oxygen further decreased the hyperventilation and increased the arterial  $P_{O_2}$  to 663 mm. Hg (range 635–685 mm. Hg). It was concluded by the authors that hyperventilation in heavy work cannot be explained simply as the result of arterial hypoxia. Earlier experiments with sudden changes from air breathing to oxygen breathing during work, and work experiments with about 12 percent oxygen in the inspired air, however, make the assumption probable that the chemoreceptor impulses elicited at the arterial  $P_{O_2}$  obtaining in the air experiments sensitize the respiratory centre towards the work stimulus. Baker and Hitchcock (1875) 1957, have studied the immediate effects on respiration in man of inhalation of 100 percent oxygen at one atmosphere. The ventilation volume is increased 6.4 percent; carbon dioxide 6.5 percent; and respiratory rate 11.5 percent. With return to normal air there are subsequently decreases of 10.5, 11.2 and 7.5 percent respectively. These effects were attributed to a partial loss of the "dual function" of hemoglobin. Increased ventilation and carbon dioxide output while breathing 100 percent oxygen was attributed to stimulation of the medullary respiratory center by increased carbon dioxide tension and increased hydrogen ion concentration. Decreased ventilation and retention of carbon dioxide resulted on a return to outdoor air from a decreased carbon dioxide tension



and hydrogen ion concentration. Chapin has pointed out that in subjects acclimatized to the altitude at Denver, Colorado there is a marked depression of ventilation during the first minute of oxygen breathing followed by a return toward normal ventilation. The magnitude and time course of transient respiratory depression by oxygen administration have also been reported by Downes and Lambertsen (1886) 1964.

The respiratory and cardiovascular effects of added external dead space while breathing air and oxygen during conditions of rest and exercise have been reported by Greenbaum (1891) 1956. During oxygen and air exposures in man the respiratory rate, tidal volume and alveolar  $P_{CO_2}$  were significantly increased with the addition of a dead space. With oxygen the increase in rate was significantly lower than with air breathing. Above dead space volumes of 2200 cc. the tidal volume and minute volume were greater in air than with oxygen, being statistically significant at 3200 cc. of dead space. With exercise, the same relationships prevailed, especially at smaller dead spaces. There was more subjective discomfort during oxygen than during air exposures. With an increase in external dead space the systolic and diastolic blood pressures rose accordingly. Significant depression of respiratory rate produced by breathing oxygen has also been observed by Greenbaum (1892) 1960, who examined the respiratory effects of breathing oxygen for 10 minutes at atmospheric pressure in both laboratory personnel and trained swimmers. The respiratory rate was depressed from 14.3 to 11.6 and from 11.6 to 9.6 breaths per minute. Respiratory minute volume was reduced from 8.3 to 7.2 and from 6.9 to 6.1 liters with no significant change in end tidal  $P_{CO_2}$ . The oxygen consumption of the swimmers was greater and the lower oxygen ventilation equivalents suggested more efficient respiration in the swimmers. An experiment by Loeschcke (1894) 1953, in which 20 persons inhaled 32 percent oxygen in 120 trials showed a temporary decrease in the resting respiratory volume on an average of eight percent in the first minute and an average increase of the alveolar carbon dioxide tension to 0.44 mm. Hg. Switching back to fresh air led to a temporary increase in respiratory volume. In studies by Shephard (1897) 1955, oxygen was

administered by the B.L.B. mask to two normal subjects and to 28 cases of congenital heart disease, and the effects on respiration were observed. The normal subjects showed a consistent increase in minute volume comparable with that previously reported by the observer. Fourteen cyanotic patients showed a very similar average response to oxygen; the other fourteen cyanotic patients tended to have a lesser response but this difference was not statistically significant. Initially at least the increase in ventilation was considered due to a greater tidal volume with little change in respiratory rate. The alveolar carbon dioxide concentration fell steeply during the first 15 minutes of oxygen administration, but there was no consistent further change at 30 minutes. This suggested that by the latter time a steady level of hyperventilation had been reached. The metabolic rate did not change with these brief periods of oxygen administration, but over a 30 minute period of administration a slight increase, perhaps irritative in type, was shown by one of the two subjects. According to the author the respiratory effects of oxygen are best explained by a reduction in chemoreceptor activity in association with a local accumulation of carbon dioxide in the respiratory center. The degree of hyperventilation observed depends on the relative magnitude of these two opposing effects.

Ernsting (1888) 1961, has studied the effect of breathing high concentrations of oxygen in producing a significant decrease in the apparent diffusing capacity and the true diffusing capacity of the pulmonary membrane. Animals breathing oxygen at one atmosphere pressure for several days develop vascular engorgement and edema of the lungs. Breathing 99 percent oxygen at one atmosphere for 24 hours caused substernal distress in 30 out of 34 men. The effects on the diffusing capacity of the lungs of breathing 100 percent oxygen for three hours was investigated in human subjects. Inhalation of 100 percent oxygen also has been shown to cause bronchoconstriction. Franck, Grandpierre and Arnould (1889) 1954, found that artificial respiration with 100 percent oxygen in urethane anesthetized guinea pigs produced distinct bronchoconstriction as determined by a manometric device. This

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## 7. EFFECTS ON METABOLISM

There appears to be no consistent and dependable evidence that breathing oxygen enriched air or pure oxygen at ambient pressures causes any change in metabolism, manifested by alterations in the exchange of respiratory gases. There are, however, a number of metabolic responses to high oxygen tension. Thus Haugard, Hess and Itskovitz (1911) 1957, studied the toxic effect of oxygen on enzyme systems in heart muscle. It was found with oxygen at a pressure of one atmosphere that there was a gradual inhibition of enzyme activity. Cupric ions in trace amounts greatly accelerated the toxic action of oxygen. The study was carried out on glucose and pyruvate oxidation in heart homogenates. Rueckert and Mueller (1915) 1960, showed that high oxygen concentrations have



powerful growth inhibiting effects on Hela cultures. Initially there was generalized reduction in the rate of cell division and in biosynthesis of DNA, RNA and protein, plus a shift of glucose metabolism to a completely anaerobic pattern and accompanying acceleration of the rate of glucose utilization. Whalen, Bosch and Dimants (1917) 1964, have discussed the limitation of oxygen consumption of isolated frog sartorius muscle by the  $P_{O_2}$ . Previous experiments suggested that the consumption of oxygen by the cell is normally limited by the  $P_{O_2}$  in the cellular environment. It was proposed that the energy from respiration above a certain basal level was converted to heat. To further test this hypothesis 32 muscles were placed in Ringers-bicarbonate solution at 22° or 27.5°C. and exposed to either 98 percent oxygen or 25 percent oxygen for six to seven hours. All gases contained two percent carbon dioxide with the balance being nitrogen. The  $Q-O_2$  of muscles in 98 percent oxygen was significantly higher than the  $Q-O_2$  of muscles in 25 percent oxygen. The ability to develop tension which was judged by occasional test contractions, was not impaired in 25 percent oxygen. The amount of lactic acid liberated from the muscles was small and was independent of the  $P_{O_2}$ . In 16 similar muscles exposed to 25 percent oxygen or to 98 percent nitrogen for five to seven hours neither the  $Na^{22}$  efflux nor the resting membrane potential differed significantly from the values obtained from paired muscles exposed to 98 percent oxygen for the same amount of time. These data are consistent with the above hypothesis. Allen (1902) 1962, has pointed out that oxygen may not be the only gaseous factor in the toxic effects on the developing chick embryos of 100 percent oxygen at one atmosphere. Fertile hen eggs incubated in an atmosphere of 20 percent oxygen with helium replacing the nitrogen showed the same retardation of development. The addition of 10 percent nitrogen is not sufficient to support adequate development of the embryo. Brosemer and Rutter (1907) 1961, have conducted experiments which indicate that growth of mammalian cells are inhibited in high oxygen tension. This inhibition may be reversed by lowering the tension within 48 hours; after longer periods of incubation irreversible changes including cellular degeneration

occur. Similar studies have been conducted by Cooper, Burt and Wilson (1908) 1958. Exposure to increasing oxygen tensions have been shown by Plaine (1913) 1955, to increase slightly but significantly the incidence of tumors in *Drosophila*.

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## 8. EFFECTS ON THE ENDOCRINE GLANDS

In a study by Bean and Smith (1918) 1953, hypophyseal and adrenocortical factors in pulmonary damage induced by oxygen at one atmosphere were examined. Hypophysectomized and nonhypophysectomized male albino rats were continuously exposed to oxygen in concentrations from 90 to about 98 percent at atmospheric pressure and in a chamber from which carbon dioxide was continuously absorbed. The non-hypophysectomized animals became dyspneic and lethargic within 20 hours of exposure and rapidly deteriorated. Several succumbed within 45 hours and all had succumbed or were killed in terminal states within 70 hours of exposure. The thoraces were filled with clear watery, bloodless fluid which clotted firmly on standing. The lungs were a deep brownish purple color, of a rubbery consistency, devoid of air and sank in fixing solution. The massive hydrothorax may help explain the decreased vital capacity commonly seen in exposures to oxygen at atmospheric pressure. In contrast to these findings none of the hypophysectomized animals succumbed and all were still active but dyspneic when killed after 70 hours of exposure. The thoraces contained little free fluid. The lungs were of essentially normal appearance and all were fully air containing. The results confirmed the earlier findings of the authors and showed how hypophysectomy protects against pulmonary damage inflicted by oxygen by eliminating or diminishing those principles which released in the normal animal augment the susceptibility of pulmonary tissues (particularly the vascular bed) to the injurious effects of oxygen in high concentrations. Corticotropin and cortical hormones constitute important parts of this augmentatory mechanism but are not essential to the precipitation of injury by oxygen. The possibility that increased carbon dioxide is a causative factor is raised by the authors.

Adrenal factors in the toxic action of oxygen at atmospheric pressure have also been considered by Smith and Bean (1921) 1955. Earlier experiments had shown that the adrenals are causally related to the toxic effects of oxygen at high pressures and that adreno-cortical and medullary factors intensified this reaction. The

same factors appear to enhance the toxic effects of oxygen at atmospheric pressure. One experimental series of 60 rats showed that adrenalectomy prolonged survival time and diminished lung damage induced by oxygen at atmospheric pressure. In a second series of 23 rats injection of cortisone (2-4 mg./rat/day) for three days prior to and during the exposure greatly enhanced lung damage and shortened survival time from 71 hours (average) for the non-injected controls to 61 hours for the cortisone injected animals. In a third series 66 rats subcutaneous injections of epinephrine (0.4 mg. at 12 hour intervals) enhanced lung damage and shortened survival time from 57 hours (average) for the controls to 43 for the epinephrinized animals. It is concluded by the authors that the protective action of hypophysectomy against the toxic action of oxygen at atmospheric pressure is due in large measure to the elimination of adreno-cortical factors, and that adrenalectomy protects by eliminating medullary as well as cortical factors, each of which when administered by itself augments the toxic action (particularly on the lungs, as manifest by vascular effects, edema, congestion and hemorrhage).

Warsaw, Molomut and Spain (1923) 1952, have shown that cortisone increases the susceptibility of mice to acute pneumonitis induced by high oxygen. Pathologic changes appeared earlier in the lungs of the cortisone treated animals and the mortality rate was accelerated. The terminal histologic findings in the lungs of the cortisone treated animals and the controls were qualitatively similar. It was suggested by the authors that cortisone is contraindicated in the treatment of acute pulmonary infections. Attention was called to the possibility that high oxygen atmospheres may be deleterious to patients receiving cortisone. The participation of hormonal reactions in the mechanism of production of pulmonary lesions has been studied in guinea pigs by Grandpierre and Grognot (1920) 1954. These animals were sustained on pure oxygen for seven, eight or nine hours. In controls lesions predominated in the lung bases, in the vicinity of the bronchi and in the subpleural zones, with thickening of the alveolar walls and compression of alveolae, swelling of cell nuclei which became round and clear, an increase in volume of the



epithelial cells whose cytoplasm became frothy and vacuolated, considerable congestion of capillaries with rare hemorrhages. In three series ACTH, cortisone and chlorpromazine were administered 30 minutes before the start of the experiment. ACTH and cortisone were found to aggravate pulmonary lesions with turgescence of the nuclei of the capillary endothelium, plasmotic leakage into the intercellular spaces which produced edema without passage into the lumina of the alveolae. However, the lesions in the cortisone animals were distinctly more severe and extensive. Chlorpromazine remarkably protected the animals against pulmonary damage. These data confirm the opinions of Bean and Smith on the role of hypophysis and adrenal cortex in the mechanism of lesions produced by oxygen inhalation; also, they demonstrate the important role of the vegetative nervous system.

Prolonged exposure to moderately increased oxygen tension can produce important changes in the function and in the tissue structures of a great number of biological systems. Gerschman, Arguelles and Ibeas (1919) 1962, have studied the gonads of young and adult hamsters and mice. They were submitted to a partial pressure of oxygen of 0.7 atmospheres under controlled conditions of temperature, humidity and of carbon dioxide content. No changes ranging to severe changes in the seminiferous elements were observed, depending on the duration of exposure (from a few days to a few weeks). Changes were seen in the intertubular spaces and in the germinal epithelium.

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## 9. EFFECTS ON COLD THRESHOLDS

MacCanon and Resnik (1927) 1963, have shown that in a relatively cool environment (22.4 to 26.5°C.) oxygen breathing increases the cold threshold from 90 microcalories/cm.<sup>2</sup>/sec. to 110 microcalories/cm.<sup>2</sup>/sec. A similar change in cold threshold was obtained at warm environmental temperatures with oxygen inhalation. Similar information is given in a paper by MacCanon and Resnik (1928) 1963. MacCanon and Eitzman (1925) 1961, determined the effects of oxygen inhalation on shivering and on thermal and metabolic responses to exposure to cold (10°C.) in ten healthy male subjects. The results showed that the oxygen breathing reduced shivering and promoted a feel of greater comfort. The ventilatory response to cold was diminished and oxygen consumption was significantly lowered during the later periods of the cold exposure. Carbon dioxide production was reduced and the mobilization of large amounts of nitrogen during shivering was also noted. Since body temperatures and their rates of fall were not significantly altered by oxygen inhalation, a shift to more efficient metabolic heat production seems to have been indicated. These results are given in more detail by MacCanon and Eitzman (1926) 1961.

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1927. MacCanon, D. M. and J. Resnik. Effect of oxygen inhalation on cold threshold. *Fed. Proc.*, 1963, 22: 341.

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## 10. EFFECTS ON MITOSIS

The following papers by Malamed (1929, 1930, 1931) 1954, 1956, 1957, deal with the effects of oxygen poisoning on the development of frog embryos. Frog legs put under oxygen

pressure develop into the normal late blastulae, but depending on the dosage of oxygen gastrulation fails to occur or is abnormal.

1929. Malamed, S. Influence of oxygen poisoning on development of frog embryos. *Fed. Proc.*, 1954, 13: 93.

1930. Malamed, S. Effect of oxygen poisoning on gastrulation of frog embryos. *Fed. Proc.*, 1956, 15: 124.

1931. Malamed, S. Gastrular blockage of frogs' eggs produced by oxygen at atmospheric pressure. *Exp. Cell Res.*, 1957, 13: 391-394.

## 11. PATHOLOGICAL EFFECTS

Bruns and Shields (1935) 1954, have demonstrated hyaline membrane in 75 percent of guinea pigs exposed to 98 percent oxygen at sea level pressure for 40-100 hours. In these animals that survive there is no residual lung damage five weeks after exposure. The pathological process from breathing oxygen has been examined radiographically by Ernsting (1938) 1960. In a study of the etiology of coughing, chest discomfort and difficulty in breathing after flight by pilots of RAF fighter aircraft this worker took chest radiographs before and after flight in a total of 42 flights. In 19 radiographs patchy areas of increased density were present in the lower lung fields immediately after landing. The syndrome appears peculiar to crew of fighter aircraft and appears to depend upon the magnitude and duration of applied positive acceleration, on the presence or absence of an anti-gravity suit installation and on the type of oxygen system used. In aircraft where post flight respiratory disturbances were common the air crew had been subjected to high positive acceleration and breathed 100 percent oxygen. The influence of the anti-gravity suit on the incidence is not clear. The condition appears to be due either to pulmonary edema or infarction. Cedergren, Gyllensten and Wersäll (1936) 1959, studied pulmonary damage caused by oxygen poisoning using the electron-microscope in mice. A condition resembling human neo-natal "hyaline membrane disease" was produced in adult mice by oxygen exposure for four to six days. Electromicroscopic studies of the damaged pulmonary tissue showed great variation. Apparently normal alveolar walls were alternating with damaged walls, atelectasis and exudate. Scattered injuries to the alveolar walls consisted of swelling of the walls, fragmentation of the basement membrane between alveo-

lar and endothelial cell layers and accumulation of exudate between the basement membrane and the alveolar or endothelial cell. It was concluded that prolonged stay in concentrated oxygen causes alveolar damage probably by increasing the transport of blood proteins and blood cells through as well as between the endothelial and alveolar cells. Experiments conducted by Grognot and Chomé (1941) 1955, on 102 guinea pigs demonstrated that after six hours of exposure to pure oxygen at atmospheric pressure there exists extensive histological reactions of the lungs, lesions consisting primarily of capillary congestion, minor hemorrhages and changes of the cells of the alveolae. These phenomena are reversible. The congestion disappears in 24 hours; the cellular distention requires a longer period to disappear. Repetition of oxygen exposure appears to be an unimportant aggravating factor, provided a free interval of about 24 hours is left between each experiment. The authors concluded that the pulmonary reactions observed are reversible in from 24-48 hours, and they stressed the early appearances of these congestive and distentive lesions which exist even without any clinical manifestations whatsoever after six hours of exposure to pure oxygen at atmospheric pressure.

Treciokas (1955) 1959, has found that white rats exposed to one atmosphere of oxygen for 38 hours, or at three atmospheres for 8 hours, show mitochondrial changes in the phagocytic alveolar cells of the lungs. Further studies of pathological changes produced by breathing oxygen have been reported by Schaffner, Lee and Schildkraut (1954) 1964. To study the effects on tissues of breathing pure oxygen, the rats were exposed to one-third, one and three atmospheres of oxygen for one week, one day and three hours respectively. On light microscopy pulmonary alveolar septa were strikingly thickened and aeration was greatly reduced. Livers, kidneys and myocardium looked normal, even with PAS and acid phosphatase stains. On electron microscopy the livers revealed increased size (partly with and partly without changes in density), and numbers of hepatocellular mitochondria often crowding out the endoplasmic reticulum. There were numerous cytolysosomes in pericanalicular zones containing degenerating mitochondria and large pinocytotic vacuoles, usually forming from or



near sinusoidal surfaces. The changes were comparable in all three groups. Previous studies had indicated that hepatocellular mitochondrial swelling, cytolysome formation and vacuolization result from hypoxia. In this study pulmonary changes account for hypoxia, but in addition mitochondrial hypertrophy and/or hyperplasia may result from the preceding hyperoxia. Thus oxygen, as used in space capsules or in hyperbaric chambers, may alter tissues first directly with increased mitochondrial mass, and secondly indirectly, by producing pulmonary changes which cause hypoxia. The influence of oxygen exposure on brain cells of mice has been studied by Gyllensten (1942, 1943) 1959. Newborn mice were exposed to concentrated oxygen at atmospheric pressure during the first 5-30 days after birth. Post-natal development of the cerebral cortex was studied by measuring the mean nuclear diameter and relative amount of internuclear material with an integration ocular. The study involved the use of control animals. In the controls there was a continuous increase of nuclear diameter in all laminae of the area striata up to the age of 20-30 days, after which a decrease of nuclear size was found. A continuous increase of the relative amount of internuclear material up to the adult age was observed. After ten days of oxygen exposure the average nuclear diameter and relative amount of internuclear material exceeded those of control animals in laminae II to VI of area striata. The combined thickness of laminae II to VI in area striata also increased. After 20 days of oxygen exposure cortical findings were reversed, that is to say there was a decrease of nuclear diameter and amount of internuclear material in the area striata, and this corresponded to a decrease of cortical thickness in the area striata.

Conger and Fairchild (1937) 1952, have reported that chromosomes have been broken in the dry pollen grains and in the microspores of the plant *Tradescantia* by exposure of the cells to partial pressures of oxygen greater than that of air. The chromosome aberrations produced are identical to those caused by ionizing radiations. Exposure to 100 percent oxygen for one hour will produce as many chromosomal aberrations as approximately 1200 r of x-rays; 65 percent oxy-

gen will produce as much effect as about 350 r. The aberrations are not caused by the methods of treatment employed, and the reactive is not photoactivated. The magnitude of the effect is related to the time of exposure and to the partial pressure of oxygen, increasing from almost no effect in air to a maximum measurable effect at 100 percent oxygen. As a final example of lesions produced by oxygen mention may be made of a paper by Gerschman, Nadig, Snell and Nye (1939) 1954. In these studies lesions were produced in the eyes of newborn mice by continuous exposure to 70 percent oxygen for 5-64 days. These lesions are suggestive of retrolental fibroplasia in human beings.

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## 12. THERAPY

The general references listed below on treatment are limited since most of the disease states referred to do not come under the scope of this Sourcebook. The reader is reminded that while short periods of oxygen breathing produce no demonstrable harm, continuous exposure for long periods will lead to severe pulmonary damage. On this basis the pulmonary limits of oxygen tolerance deserves the most serious attention in therapy.

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## B. EFFECTS OF OXYGEN TENSION IN EXCESS OF ONE ATMOSPHERE

### 1. GENERAL STUDIES

Breathing oxygen under pressures above 1.0 atmosphere for a sufficiently long time and at sufficiently high pressure eventually leads to the development of oxygen toxicity characterized by general convulsions. The cause of these convulsions is not yet completely understood in spite of considerable investigation in this field. The effects of oxygen tension in excess of 1.0 atmosphere are significant not only as they bear upon



the causes, course and treatment and prevention of oxygen toxicity, but also because of their relevance to hyperbaric oxygenation as a therapeutic modality in certain disease conditions.

It has been shown that oxygen in high percentages and at ambient pressure acts as a local irritant, but oxygen toxicity occurs under high pressure in too brief a period for an irritant effect to be causative as Lambertsen (1977) 1961, has stated. Oxygen poisoning is reversible (except in cases of unconsciousness in SCUBA diving) although sufficiently prolonged breathing of oxygen at high pressure leads to death of experimental animals. Oxygen toxicity, as stated, is a function of pressure and duration. The safe period for oxygen breathing is reduced by immersion and exercise. Tolerance is also reduced by carbon dioxide inhalation. Current evidence reveals no carbon dioxide accumulation in the brain at the time of oxygen convulsions nor any effect on brain tissue slices nor conduction in peripheral nerves. The carbon dioxide accumulation does, however, cause vasodilatation in the brain which increases the effect of oxygen and also interacts with it to have an obscure effect on the pulmonary toxicity of oxygen. High oxygen pressure interferes with oxidative processes especially through inactivation of enzymes in which sulfhydryl groups are essential.

It has been pointed out (1982) 1959, that high pressure oxygen poisoning affecting the brain and causing convulsions can definitely occur at 2.0 atmospheres and sometimes at even lower pressures. Oxygen poisoning is a concern not only in diving, but in its use in decompression with helium-oxygen and in the treatment of decompression sickness. The latent period to the onset of oxygen poisoning is shortened by exertion and by excess carbon dioxide, as has been stated. Oxygen tolerance has inter- and intra-individual variation. Warning symptoms in order are: muscular twitching, nausea, abnormalities of vision and hearing, difficulty in breathing, anxiety and confusion, unusual fatigue, incoordination and convulsions. The convulsions are not in themselves dangerous but result in tongue chewing, brusing, air embolism (if diver is rapidly brought to the surface) and drowning (particularly with the use of SCUBA gear). The convulsions are usually self-terminating, even if

the same partial pressure of oxygen is maintained. They are followed by a quiet phase of a few moments; there are apparently no lasting effects. The mechanism of oxygen poisoning, although presently obscure, may be considered to be a direct effect through interference with enzyme systems. For a further general paper on high pressure oxygen, including therapeutic potentials of hyperbaric oxygenation, a U.S. NRC Report (1983) 1963, should be consulted. Oxygen under high pressure appears useful when an increased gradient of oxygen transfer is required. It cannot deal directly with hypoxic anerobic metabolism. There are practical limitations and lung damage and convulsions are to be kept in mind. There is an approximately two percent incidence of convulsions upon breathing oxygen at 2.8 atmospheres for two hours. Removal of carbon dioxide from combination with hemoglobin is accelerated by oxygen under high pressure. The indications for the use of oxygen under high pressure are increasing. (It is perhaps beneficial in barbiturate poisoning. It is used as an adjunct to radiation therapy in the treatment of malignant tumors. It has also been utilized in the treatment of gas gangrene infections). More proof of its true value is needed. Such proof must be derived from clinical investigation under rigid controls. The oxygen reservoir effect of oxygen under high pressure for cardiac surgery is likely to be disappointing since the arterial  $P_{O_2}$  is only brought toward normal. Oxygen under high pressure may be beneficial as an emergency measure in traumatic peripheral vascular insufficiency, but could be of doubtful benefit in peripheral vascular disease. It is possible that oxygen under high pressure has a potential application in coronary occlusion. The value of oxygen under high pressure in cerebral vascular disease may be greatest in the extracranial form, i.e. carotid arterial obstruction. It is said to be of distinct benefit in hemorrhagic shock. Carbon monoxide poisoning and acetanilide poisoning have both been treated successfully with oxygen under high pressure.

The possibility of oxygen toxicity imposes serious tactical problems in certain naval maneuvers, for example: underwater demolition team swimmers are enabled, through the use of a closed circuit breathing apparatus where the oxygen is

recirculated and the carbon dioxide is absorbed, to swim underwater to their objective with maximum stealth. Not only can they remain underwater but also no bubbles reach the surface to invite visual detection of their presence. In such operations the swimmers can swim for a prolonged period of time without oxygen intoxication as long as they do not swim deeper than the ten foot depth. If deeper swimming is attempted the danger of toxic effects escalates rapidly. For example, if a swimmer convulses at depths below ten feet the convulsions will not in themselves be lethal but he will in all probability lose his mouthpiece and drown (quite apart from the fact that he is seriously disabled).

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## 2. EFFECTS ON THE CENTRAL NERVOUS SYSTEM

Gowdey and Patel (1989) 1962, have studied convulsions and other effects induced in conscious rats by oxygen under high pressure and have examined the effects of repeated exposure to oxygen. A month after the implantation of electrodes in the skull each rat was placed in a sling and then compressed with oxygen in a small chamber (with a carbon dioxide absorber) at 10 psi per minute to a level of 60 psi (gauge). They were maintained at this level until at least three convulsions occurred and they were then decompressed in stages. The frequency of the EEG usually decreased and the amplitude increased before and immediately after the convulsions. Respiratory rate and depth increased; body temperature was maintained fairly constant. In a first series 14 rats were exposed on five successive weeks and the time to first convulsions (CT) recorded. After an initial rise at the second exposure the CT fell and was below normal at the fifth exposure. Hemoglobin values were above controls and extensive lung damage was seen. Series II consisted of five groups (10 rats each) which were exposed on six successive weeks to 60 psi (gauge) of oxygen, or air, two percent carbon dioxide in oxygen or to normal pressure of oxygen or of air. The CT was shorter in the carbon dioxide group than in the oxygen group; and the CT in both groups increased slightly for four exposures and then began to fall. No significant lung damage could be found. No convulsions occurred at normal pressure. Five rats were exposed to oxygen at 60 psi (gauge) until respiration ceased (after some two-and-a-half hours and 50 convulsions). Moruzzi (1993) 1954, has shown that following breathing of pure oxygen at high pressure both cortical and subcortical structures show electrical patterns similar to those observed during epileptic seizures in man. In the unanesthetized cat these patterns resembled those observed during the tonic phase of grand mal. In the same species under urethane anesthesia the same high levels of oxygen pressure produced



instead only clonic convulsions. The repetition rate of both motor and cortical phenomena is clearly increased by sensory stimuli.

Mantegazzini (1992) 1954, has studied the effects of oxygen respiration at high pressure on the electrocorticogram as well as on the response of the visual cortex to stimuli applied to the optic nerve. These studies were done in unanesthetized rabbits before and after ponto-mesencephalic section. In intact animals, after 10–30 minutes respiration of oxygen at 5.0 to 6.0 atmospheres there occurred seizures resembling those of human “grand mal” type with typical EEG registration. Decompression did not immediately interrupt the course of the attack. Section of the brain stem at the upper margin of the pons did not modify the EEG convulsive picture produced by hyperoxia. In the “isolated brain” preparations the response of the visual cortex to stimulation of the contralateral optic nerve was not modified either before or during the seizures. High frequency stimulation of the optic nerve was incapable of causing seizures and, if this was occasionally followed by a spontaneous attack, the convulsive activity did not appear more in the contralateral visual cortical area than in other cortical areas. These latter observations indicated to the author that the cerebral cortex in the pre seizure and inter seizure phases is not susceptible to the toxic action of oxygen, which serves to sustain the hypothesis that hyperoxic convulsions are of subcortical origin.

Perot (1994) 1956, has drawn attention to reports describing toxicity of oxygen at high pressure on nerve muscle preparations. These studies give no direct evidence of functional impairment of the nerve *per se*. In the author's studies frog sciatic and cat ulnar nerves were stimulated continuously (20 pulses/second; voltage supramaximal for alpha fibers) in a pressure chamber at 13 atmospheres absolute oxygen. Changes in action potential amplitude were studied. Each nerve's initial action potential amplitude was made the same by amplifier adjustment and conduction block was defined as the disappearance of the action potential during continuous stimulation with the initial parameters. Complete conduction block occurred in all nerves tested. The mean time for the block in frog nerves at 13 atmospheres oxygen was

four-and-a-half hours; in a five percent carbon dioxide–95 percent oxygen mixture at 13 atmospheres it was three hours. The block was partially reversible on return to room pressure if it had not been maintained for more than a few minutes. The presence or absence of continuous stimulation did not affect the time course of conduction block. Cat nerves maintained in Tyrode's solution, with no added carbon dioxide prior to exposure to oxygen under high pressure, were blocked in 13 atmospheres oxygen in 2.25 hours. Cat nerves maintained in Krebs-Henseleit solution equilibrated with five percent carbon dioxide and 95 percent oxygen before exposure to 0.38 percent carbon dioxide and 99.62 percent oxygen at 13 atmospheres (to maintain an approximate physiological carbon dioxide tension during exposure) were blocked in 50 minutes at 37°C. Recovery was poor or else not evident. The data indicate that oxygen under high pressure is directly toxic to peripheral nerves, and that the mammalian nerve is more susceptible than the frog nerve. Kaufman, Owen and Lambertsen (1990) 1956, have stated that the convulsions caused by oxygen inhalation at increased ambient pressures occur only after a latent period free of signs or symptoms of oxygen toxicity. In the present investigation the authors explored the effect of brief interruptions of oxygen breathing upon the total duration of oxygen exposure required to produce toxicity. Twenty-two control guinea pigs were exposed continuously to 100 percent oxygen at 3.0 atmospheres. At the same pressure 22 other guinea pigs breathed 100 percent oxygen for 30 minutes or 7 percent oxygen in nitrogen (equivalent to the  $P_{O_2}$  of 21 percent oxygen at 1.0 atmosphere) for 10 minutes and continued this alternation for the duration of the experiment. The levels of inspired carbon dioxide did not exceed 0.1 percent for either group. In the control guinea pigs exposed continuously to 100 percent oxygen, the first animal developed toxicity at three hours, while the mean latent period for the group was 5.2 hours. The first sign of toxicity in the intermittently exposed group occurred at 9.6 hours (oxygen time 7.2 hours), with a mean time for this group of 17.0 and 12.8 hours respectively. This increased tolerance to 3.0 atmospheres of high oxygen was significant and indicates that the rate of recovery

from the central nervous system manifestations of oxygen poisoning exceeds the rate of their development. In addition to extending oxygen tolerance at increased pressure, the alternation of high and low  $P_{O_2}$  allowed elimination of nitrogen during the periods of oxygen breathing and prevented the development of 'bends' up to 25 hours total exposure at 3.0 atmospheres pressure.

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### 3. EFFECTS ON MUSCLE

Gilbert and Lowenberg (2001) 1963, have examined the effects of high oxygen pressure on the resting membrane potential of the sartorius muscle in the frog. The effect of high oxygen pressure on the resting muscle membrane potential was measured by the use of a microelectrode. From each frog one muscle was subjected to an experimental condition and its contralateral served as a control. Muscles were immersed in solutions buffered with 50 mM. of tris (hydroxymethyl) aminomethane. Control potentials were about 90 mV. Thirty minutes after exposure to 140 atmospheres oxygen for two hours, the experimental value was still  $98.5 \pm 0.8$  percent of its control. However, three hours after the oxygen exposure the value was only  $90.3 \pm 0.95$  percent. Exposure to 140 atmospheres of nitrogen produced no such effects. When 3.26 mM. reduced glutathione was added to the solutions after exposure to oxygen this decrease was inhibited. Immersion of muscles in 1.0 mM. of hydrogen peroxide for four hours had no influence upon the membrane potential. Similar immersion in 50 mM. of hydrogen peroxide did decrease the potential to  $93.8 \pm 0.49$  percent of its control.

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### 4. EFFECTS ON HEART AND CIRCULATION

Breathing oxygen at pressures higher than 1.0 atmosphere causes a reduction of pulse rate and diminution of cardiac output. There are also changes in the circulation of regional vascular beds. Thus, as oxygen tension increases there is cerebral and coronary vasoconstriction. Vasoconstrictor effects are also found in the human eye, in the kidney and possibly in the skin. These



effects may be due to a direct action of oxygen on vascular smooth muscle and in addition the influences of a central increase in carbon dioxide as well as neurogenic and chemical factors may play a part. If the arterial carbon dioxide is maintained constant as oxygen is administered to normal human subjects at one atmosphere cerebral vasoconstriction is not observed. Thus it has been suggested that cerebral vasoconstriction in normal subjects is caused by arterial hypercapnia that accompanies the respiratory stimulation produced by oxygen.

Lambertsen, Kough, Cooper, Emmel, Loeschcke and Schmidt (2006) 1953, found that at 3.5 atmospheres oxygen inhalation produced a 55 percent increase in cerebral vascular resistance resulting in a 25 percent reduction in the rate of blood flow through the brain. When compared with oxygen inhalation at 1.0 atmosphere, changes were twice as great but not statistically different. Dissolved oxygen in arterial blood at 3.5 atmospheres averaged 6.5 volumes percent, but more oxygen was given up to the brain tissues because of slower cerebral blood flow resulting in an average internal jugular hemoglobin saturation of 89 percent. Removal of physically dissolved oxygen as blood passed through the brain lowered the  $P_{O_2}$  by 2000 mm. Hg. Partial interference with oxyhemoglobin reduction rendered carbon dioxide transport less efficient. This, plus slower flow rate accounted for an 8 mm. Hg increase in the A-V  $P_{CO_2}$  difference across the brain. A 5 mm. Hg fall in arterial  $P_{CO_2}$  limited venous increase to 3 mm. Hg. This is not compatible with a concept of increased brain tissue  $P_{CO_2}$  as contributing to oxygen toxicity, but rather of reduced exposure of brain tissue to toxic levels of oxygen tension by producing hyperventilation and cerebral vasoconstriction. No alteration in the rate of oxygen consumption or the respiratory quotient of the brain could be detected at 3.5 or 1.0 atmosphere of inspired oxygen. In studies reported by Schaefer (2013) 1953, twelve trained underwater swimmers swam at a speed of about 0.85 knots at the surface and at 20, 30 and 40 feet depth, while breathing oxygen for a period of 93 minutes with rest periods after each 15 minutes. The water temperature at the surface was 80°F. and the underwater tempera-

ture was 90°F. The average pulse rate, measured at the beginning of rest periods, showed a consistent decline with continuing exercise at each depth, exhibiting the well-known bradycardia effect of oxygen, whereas the average respiratory rate showed an upward trend. The average pulse rate and respiratory rate at the end of swims terminated because of symptoms were significantly higher than those at the end of normally terminated swims, suggesting that an increased sympathetic activity accompanies symptoms of oxygen toxicity. Pulse rate measurements at the beginning and end of rest periods made possible the demonstration of a sign of predominant parasympathetic activity, namely the fixation of pulse rate or nonresponsiveness of pulse rate to change from exercise to rest or from rest to exercise. This sign preceded the development of symptoms in 78 percent of the cases and can be used by the swimmer as a warning for acute symptoms of oxygen toxicity. Under conditions of underwater swimming while breathing oxygen dyspnea is the most frequent symptom in contrast to resting conditions at high oxygen tension. The dyspnea was usually characterized by rapid, shallow breathing and apparent inspiratory inhibition. For a further report on cardiac slowing and respiratory rate changes under high oxygen pressure in rats, the report by Taylor (2016) 1958, may be consulted. Whitehorn and Bean (2017) 1952, in 18 decerebrate dogs also observed a pronounced decrease in heart rate as well as a slowing of cardiac conduction manifested by a prolonged P-R interval. Decreased amplitude of the P wave and increased T wave were common. With short exposure these effects were largely reversible. With prolonged exposure slowed conduction progressed to A-V block with suppression or extinction of the P wave, accompanied by ventricular extrasystoles and nodal rhythms. There was only partial and transient recovery, if any. In animals that succumbed respiration was arrested before the heart. Vagotomy and/or stellatectomy postponed OHP changes but did not prevent them.

Aschan and Wallenius (2003) 1953, have reported that guinea pigs exposed to oxygen poisoning showed transudation into the tympanic cavity, the paranasal sinuses and the pleuropericardiac cavity. These transudates had a protein

composition strongly resembling that of serum and indicated grave alterations of vascular permeability.

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## 5. EFFECTS ON THE BLOOD

Taylor (2022) 1957, has shown that gross hemolysis occurs in vitamin E deficient rats exposed to 5.0 atmospheres of pure oxygen. Protection against this hemolysis is given by tocopherols in large doses.

Boerema, Meijne, Brummelkamp, Bouma, Mensch, Kamemans, Stern Hanf and Aalderen (2018) 1960, have shown in young pigs that the hemoglobin level can be lowered to a level of 0.4 percent by exchanging blood for plasma. In this virtually hemoglobin-free state normal physiologic functions are still possible if the animals are subjected to oxygen at 3.0 atmospheres in the high pressure tank. In such a situation most of the oxygen transport uses the mechanism of simple solution in the plasma. These animals could not live at normal atmospheric pressures but recovered uneventfully after re-infusion of normal blood.

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## 6. EFFECTS ON RESPIRATION

If oxygen is given to human subjects at sea level there is an initial transient reduction in



ventilation which is supplanted within approximately one minute to a moderate respiratory stimulation. Concurrently the slope of the ventilatory response to carbon dioxide inhalation decreases; therefore stimulant and depressant effects of oxygen can exist together. It appears that the respiratory response to carbon dioxide is reduced more by oxygen inhalation at pressures of 2.0 and 3.0 atmospheres than at 1.0 atmosphere. In spite of its depressant effects on mechanisms of respiration normal subjects breathing oxygen at a pressure of 1.0 atmosphere or more show an overall increase in alveolar ventilation. This increase appears to be a result of the rise in central  $P_{CO_2}$  and hydrogen ion concentration and supervenes when high oxygen pressures interfere with carbon dioxide transport from the tissues.

Lambertsen, Stroud, Gould, Kough, Ewing and Schmidt (2029) 1953, reported that breathing oxygen at 3.5 atmospheres lowered alveolar  $P_{CO_2}$  6.7 mm. of Hg and produced an increase in respiratory minute volume of about 26 percent due to a greater tidal volume with no elevation in respiratory rate. There was a slight rise in carbon dioxide elimination. Breathing six percent oxygen (equivalent to 21 percent oxygen at sea level) at 3.5 atmospheres lowered the alveolar  $P_{CO_2}$  1.3 mm. Hg as the only demonstrable effect, indicating that respiratory stimulation at increased ambient pressures is due to the oxygen and not to increased density of the inhaled gas. Breathing air at 3.5 atmospheres lowered the alveolar  $P_{CO_2}$  2.5 mm. Hg and produced no other significant changes. The relation to oxygen toxicity, the efficiency of alveolar ventilation at increased ambient pressure and the underlying causes of the respiratory stimulation by high inspired oxygen tensions are discussed in this paper. The most likely cause of oxygen hyperpnea appears to be central accumulation of carbon dioxide resulting from decreased reduction of oxy-hemoglobin.

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## 7. EFFECTS ON BLOOD AND TISSUE GAS TENSIONS

Breathing oxygen at high atmospheric pressures results in a rise in blood and tissue oxygen tensions. Bahnson and Matthews (2030) 1953, studied oxygen poisoning with gas bubble analysis plus arterial blood studies in rabbits and rats. During exposure to 1.0 atmosphere of oxygen there was no significant change in tissue oxygen and carbon dioxide until there was evidence of pulmonary damage and change in arterial gas content. At 7.0 atmospheres the carbon dioxide rose quickly to approximately 66 mm. Hg and was maintained for approximately 12–15 minutes. After 15 minutes the  $P_{CO_2}$  rose further. A change in the carbon dioxide combining power of the blood was demonstrated. According to Bean (2032) 1961, shifting from breathing air to oxygen at atmospheric pressure in dogs and cats caused a well maintained reversible increase of available oxygen in the tissues. Subsequent compression of the oxygen to as high as 80 psi caused a further prompt and more pronounced elevation in tissue oxygen which was maintained well above the pre-compression value throughout the period of exposure (20 to 45 minutes) and on to the onset of convulsive seizures. These changes were also reversible. Occasionally, in prolonged exposures, there was a late very gradual decline, especially where there was lung damage. Essentially similar results were obtained by using sodium pentobarbital. These experiments

involved continuous polarographic recordings from the brains of the animals anesthetized with morphine and urethane. These studies are reported in more detail by Bean (2031) 1961. A shift from breathing air to breathing oxygen at atmospheric pressure or at 5.0 atmospheres raised the availability of oxygen to the brain. Decompression reversed these effects. The author stated that cerebral vasoconstriction which may have occurred in oxygen under high pressure was apparently insufficient to prevent pronounced elevation of cerebral oxygen or to protect against oxygen toxicity. In simultaneous recordings from two regions of the brain the occurrence of cyclic changes, frequently out of phase, suggested the involvement of a reciprocating cerebral vascular control mechanism between different regions. Addition of carbon dioxide to the OHP to give concentrations of 0.8 to 1.7 percent usually raised the oxygen availability and tended to precipitate asynchronous cyclic oxygen changes. Apparently the vasculature does not necessarily react *en masse* to carbon dioxide. It is suggested that jugular venous blood is not a reliable index because of wide variations in  $P_{O_2}$ ,  $P_{CO_2}$  and pH in circumscribed regions of the brain. Such regions may serve to precipitate manifestations of oxygen toxicity. Jamieson and Van Den Brenk (2034) 1963, have measured brain and cerebrospinal oxygen tensions in rats breathing air or in various high pressures of oxygen. Addition of five percent carbon dioxide to the inspired oxygen raised the cerebral oxygen tensions when the rats were exposed to 2.0 atmospheres or above. Lambertsens, Ewing, Kough, Gould and Stroud (2035) 1955-56, found in four human subjects that additions of two percent carbon dioxide to oxygen inhaled at 3.5 atmospheres caused an average increase of internal jugular venous  $P_{O_2}$  of nearly 1000 mm. Hg above the level found during the breathing of oxygen alone. The relation of this finding to changes in brain  $P_{O_2}$  and to oxygen toxicity are discussed. The authors propose that an increased tension of inspired carbon dioxide shortens the latent period of oxygen toxicity, not by direct action on brain cells, but indirectly through a cerebral vasodilatation and the resulting rise in brain  $P_{O_2}$ . The relationships of respiratory minute volume to arterial and internal jugular venous blood  $P_{CO_2}$  and pH during inhala-

tion of low concentrations of carbon dioxide at 1.0 atmosphere and oxygen at 3.0 atmospheres have been reported by Lambertsens, Kough, Cooper, Emmel, Loeschcke and Schmidt (2036) 1953. During oxygen breathing at 3.0 atmospheres an average rise of 3 mm. Hg internal jugular  $P_{CO_2}$  was accompanied by about a 30 percent increase in the respiratory minute volume. Average results obtained in eight men breathing 0.0, 2.2, 4.3 and 5.5 percent carbon dioxide in 21 percent oxygen at 1.0 atmosphere indicate that at about two percent inspired carbon dioxide there occurs a significant increase in the slope of the curves relating respiratory minute volume to arterial  $P_{CO_2}$  or pH and to internal jugular venous  $P_{CO_2}$  or pH. Above this region the respiratory minute volume versus  $P_{CO_2}$  curves are essentially linear. The curve relating respiratory minute volume to arterial  $P_{CO_2}$  has a slope of 1.26 liter/minute/ $m^2$ /mm. Hg rise in  $P_{CO_2}$ , while the corresponding value for respiratory minute volume versus internal jugular  $P_{CO_2}$  is 1.76. Arterial and venous curves therefore converge slightly with increasing ventilation.

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2036. Lambertsens, C. J., R. H. Kough, D. Y. Cooper, G. L. Emmel, H. H. Loeschcke and C. F. Schmidt. Relationships of respiratory minute volume to arterial and internal jugular venous blood  $pCO_2$  and pH during inhalation of low concentrations of  $CO_2$  at one atmosphere and  $O_2$  at 3.0 atmospheres. *Fed. Proc.*, 1953, 12: 81.



2037. Sonnenschein, R. R., S. N. Stein and P. L. Perot, Jr. Oxygen tension of the brain during hyperoxic convulsions. *Amer. J. Physiol.*, 1953, 173: 161-163.

#### 8. EFFECTS ON THE ALIMENTARY TRACT

Cross (2038) 1954, has studied the effects of increased atmospheric pressures and the inhalation of 95 percent oxygen and helium-oxygen mixtures on the viability of the bowel wall and the absorption of gas in closed-loop obstructions. The rate of diffusion of gas from closed-loop obstructions was increased by means of increased atmospheric pressure *per se*. The most satisfactory schedule for the absorption of gas from closed-loop obstructions in terms of maximal absorption in minimal time was the use of 95 percent oxygen at 2.0 atmospheres pressure for six hours. This schedule resulted in the absorption of 44.8 percent of the injected air. Oxygen intoxication became a significant factor in Cross' studies in those dogs inhaling 95 percent oxygen when the pressure was increased above 2.0 atmospheres in a six hour period and when the time of exposure extended beyond six hours at 2.0 atmospheres pressure. Helium-oxygen mixtures were not found to be an effective substitute for 95 percent oxygen, because helium diffused into the bowel as the nitrogen diffused out, thereby partially maintaining the distention of the closed loops. The viability of the bowel in closed-loop obstructions was well preserved for periods up to 92 hours by the use of increased atmospheric pressures.

2038. Cross, F. S. The effect of increased atmospheric pressures and the inhalation of 95 per cent oxygen and helium-oxygen mixtures on the viability of the bowel wall and the absorption of gas in closed-loop obstructions. *Surgery*, 1954, 36: 1001-1026.

2039. Cross, F. S. and O. H. Wangenstein. The effect of increased atmospheric pressures on the viability of the bowel wall in the absorption of gas in closed-loop obstruction. *Surg. Forum*, 1953, 4: 111.

2040. Frittelli, G., E. S. Tank, W. F. Bernhard and R. E. Gross. A study of ileus under hyperbaric conditions. *Surg. Forum*, 1963, 14: 376.

#### 9. EFFECTS ON METABOLISM

For a good review of the toxic effects of oxygen on the metabolism of nervous tissue, a chapter by Dickens (2045) 1962, should be consulted. This excellent paper covers the early literature and some recent literature. The reader is referred especially to the section on oxygen at pressures above one atmosphere, dealing with

the toxic effect of oxygen on brain tissue and respiration. A comparison is given of the sensitivity of the brain to oxygen under high pressure with that of other tissues. There is a discussion of the possible relationship between oxygen toxicity and irradiation effects, the effects of various hormones, vitamins and autonomic drugs on oxygen poisoning, as well as the toxic effects of oxygen on isolated enzyme systems and the possible role of hydrogen peroxide in oxygen poisoning.

In referring to oxygen toxicity, consideration is often given primarily to effects on the nervous system and particularly to the development of convulsions. However, there may be earlier toxic effects in other tissues but the subtle changes in metabolism in these tissues may not be so readily recognized by behavioral and symptomatic manifestations. Reference has been made to the effect that the latent period for convulsion development is shorter than that for enzyme inhibition to change metabolism in the test tube. This again may suggest that very subtle chemical changes can affect the electrical activity of the nervous system in its highly organized behavior. As Lambertsen has stated (*Fundamentals of Hyperbaric Medicine*, Publication No. 1298, National Academy of Sciences, National Research Council, Washington, D.C., 1966, page 25), the effects of oxygen on membranes, not directly paralleled by changes in the oxidative metabolism of cell systems, are responsible for the convulsions. The discrepancy between *in vitro* and *in vivo* studies is seen by Lambertsen to be still more pronounced when it is recognized that at a given elevated ambient  $P_{O_2}$  the cells of an *in vitro* homogenate are exposed to a rather uniform oxygen tension, whereas while only a very small portion of the cells in the brain of an intact animal are exposed to this high oxygen tension.

As Sullivan and Bean (2057) 1957, have stated, the elevation of blood sugar in exposures to oxygen at high pressures (OHP) suggests that the protection afforded by hypophysectomy and adrenalectomy against OHP might be explained by an attendant lowering of blood sugar, especially since the medullary factor (adrenalin) which elevates blood sugar was previously shown to enhance the oxygen toxicity as did insulin.

These authors therefore made an attempt to determine what effect preliminary elevation of blood sugar would have on the toxicity of oxygen under high pressure. Large mature male Sprague-Dawley rats were selected in pairs of one test and one control. The test rats were injected intraperitoneally with 1 cc. of a 33 percent glucose solution; the controls were injected with 1 cc. of physiological saline. Blood sugars of test and control animals were then determined colorimetrically immediately before (and after) their exposure to oxygen at 90 pounds pressure for about 20 to 40 minutes. They were then decompressed in stages, sacrificed under pentothal anesthesia and the lungs were removed, grossly examined and weighed. It was found that in the test rats the neuromuscular reactions were more delayed in onset, fewer in number, less severe and the mortality less than in the controls, as was also the lung weight. It would appear to the authors therefore that elevation of glucose preceding exposure provides some protection against OHP and that the initial elevation of glucose induced by OHP is a part of a defense mechanism operating through the hypothalamus and sympathetics which when pushed too far becomes a liability, for reasons other than glucose changes alone.

In a study on chemical mechanisms in oxygen toxicity Thomas and Neptune (2059) 1963, examined the production of labeled carbon dioxide from labeled glucose using mitochondria from rat brain homogenates. The homogenates were fortified with DPN<sup>+</sup>, ATP, hexokinase, KCl and Mg to stimulate maximum carbohydrate metabolism. The experiment was carried out at 0.2, 1.0 and at 5.0 atmospheres (absolute) and lasted 30 minutes. Large increases in lactate were seen at 5.0 atmospheres, accompanied by large increases in pyruvate and a slight decrease in glucose utilization. The production of labeled carbon dioxide was diminished at 5.0 atmospheres. The addition of the cofactors CoA and TPP did not alter the inhibition by increased oxygen, nor did high concentrations of catalase or GSH. The authors concluded that oxygen under high pressure inactivates enzyme systems. Two types may be concerned: 1) slow and irreversible inactivation of certain enzymes where oxygen acts directly on certain protein apoenzymes. This may

be related to the slowly fatal and irreversible effects of oxygen *in vivo*; 2) rapid and reversible inhibition of specific enzyme systems by the action of OHP on essential cofactors such as alpha lipoic acid related to reversible neurotoxic effects *in vivo*. Oxidation of SH groups are usually involved. For a further study of the effect of high oxygen tensions upon enzymes a report by Haugaard (2054) 1955, should be consulted. The effects on phosphatase are described by Becker and Sutton (2044) 1963, and a possible method of action of oxygen poisoning is presented by Gerschman (2047) 1954. The author hypothesizes that the primary underlying mechanisms of oxygen poisoning are similar in principle to X-irradiation, viz., possibly formation of oxidizing free radicals, OH, O<sub>2</sub>H and H<sub>2</sub>O<sub>2</sub>. Barron (2042) 1955, carried out experiments on the rate of oxidation by OHP of certain -SH compounds and other oxidation-reduction systems of biological interest. Nonprotein sulfhydryl groups (glutathione, cysteine, coenzyme A) were rapidly oxidized by oxygen, the rate being proportional to the oxygen pressure. The -SH groups of yeast alcohol dehydrogenase were also oxidized by OHP, and the enzyme activity was inhibited. The oxidation of unsaturated fatty acids, of hemoglobin and of dihydrodiphosphopyridine nucleotid was not affected by OHP. The author postulated that the harmful effects of oxygen are due mainly to the oxidation of the -SH groups which are necessary for the cell activities. Gilbert, Gerschman, Ruhm and Price (2053) 1957-58, have considered the production of hydrogen peroxide in solutions of glutathione exposed to oxygen. Gilbert, Gerschman and Fenn (2052) 1956, have reported on the effects of OHP in *in vitro* systems. Exposure of DNA in the presence of reduced glutathione to OHP for about 12 hours results in a viscosity decrease with a net formation of hydrogen peroxide. Further work has shown that when 3.26 mM of reduced glutathione per liter was exposed to 6.0 atmospheres for about 14 hours only about one-third was oxidized, but at 130 atmospheres oxygen no reduced glutathione was detectable. It was of interest to the authors to investigate the effects of adding various agents which have been used in *in vivo* oxygen toxicity studies, to these *in vitro* systems. Thiourea was found to inhibit the net



formation of hydrogen peroxide in reduced glutathione solutions exposed to OHP, and also restrained the fall in viscosity produced by OHP in the DNA solution containing reduced glutathione. Thiourea also inhibits the viscosity decreases of DNA resulting from X-irradiation. In mice thiourea has been reported to protect against OHP and X-irradiation. EDTA, a known chelating agent, also prevents the fall in viscosity of solutions containing DNA and reduced glutathione when exposed to OHP. EDTA at a concentration of 0.3 micromoles/liter prevents the oxidation of reduced glutathione exposed to OHP, which would strongly indicate that its action is due to removal of trace metals. Yet to decrease oxidation of reduced glutathione 3 millimols/liter diethyldithiocarbamic acid sodium salt, another chelating agent, was necessary. The suggestion that some chelating agents may be free radical receptors should be given consideration, according to the authors, in attempting to interpret these results.

Studies by Gerschman, Gilbert and Frost (2048) 1958, upon paramecia have shown that treatment with cobalt chloride or with manganese chloride increases the survival times of these organisms at 9 atmospheres and decreased them at 2 atmospheres oxygen pressure. For another basic biological paper, a report by Falsetti (2046) 1959, may be consulted. This author found that oxygen at 8-12 atmospheres (absolute) depresses the transport of sodium ions across the isolated frog skin. The addition of 8-10 atmospheres of nitrogen without oxygen deprivation had no such effect. These observations are consistent with the idea that excess oxygen interferes with the normal activity of oxidative enzymes and inhibits sodium transport by diminishing the supply of enzymes available for the purpose.

2041. Barker, J., C. E. Quartley and E. R. Turner. Studies in the respiratory and carbohydrate metabolism of plant tissues. IX. Experimental studies of the influence of oxygen at high pressures on the respiration of apples and of a "block" in the tricarboxylic acid cycle induced by "oxygen poisoning." *Proc. roy. Soc.*, 1960, 152: 88-108.

2042. Barron, E. S. G. Oxidation of some oxidation-reduction systems by oxygen at high pressures. *Arch. Biochem. Biophys.*, 1955, 59: 502-510.

2043. Becker, N. H. and B. F. Galbin. Effect of oxygen rich atmospheres on cerebral lipid peroxides. *Aerospace Med.*, 1962, 33: 985.

2044. Becker, N. H. and C. H. Sutton. The histochemical effects of oxygen at high pressures. pp. 152-165 in: *Second symposium on underwater physiology*. Edited by C. J. Lambertsen and L. J. Greenbaum, Jr. National Research Council, Washington, D.C. N.R.C. Publication 1181, 296 pp.

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2049. Gerschman, R., D. L. Gilbert, S. W. Nye, P. Dwyer and W. O. Fenn. Oxygen poisoning and x-irradiation: a mechanism in common. *Science*, 1954, 119: 623-626.

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2052. Gilbert, D. L., R. Gerschman and W. O. Fenn. Effects of high oxygen pressure (HOP) in *in vitro* systems. *Fed. Proc.*, 1956, 15: 73.

2053. Gilbert, D. L., R. Gerschman, K. B. Ruhm and W. E. Price. The production of hydrogen peroxide by high oxygen pressures. *J. gen. Physiol.*, 1957, 41: 989-1003.

2054. Haugaard, N. Effect of high oxygen tensions upon enzymes. pp. 8-12 in: *Proceedings of the underwater physiology symposium*. Edited by L. G. Goff, National Research Council, Washington, D. C. N.R.C. Publication 377, 1955, 153 pp.

2055. Haywood, C., H. C. Hardenberg, Jr. and E. N. Harvey. The effect of increased pressures of oxygen upon the luminescence of *achromobacter fischeri*. *J. cell. comp. Physiol.*, 1956, 47: 289-293.

2056. Jamieson, D. and H. A. S. Van Den Brenk. Pulmonary damage due to high pressure oxygen breathing in rats. 2. Changes in dehydrogenase activity of rat lung. *Aust. J. exp. Biol. med. Sci.*, 1962, 40: 51-56.

2057. Sullivan, L. P. and J. W. Bean. Blood glucose in exposures to oxygen at high pressures. *Fed. Proc.*, 1957, 16: 125.

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2059. Thomas, J. J., Jr. and E. M. Neptune, Jr. Chemical mechanisms in oxygen toxicity. pp. 139-151 in: *Second symposium on underwater physiology*. Edited by C. J. Lambertsen and L. J. Greenbaum, Jr. National Research Council, Washington, D.C. *N.R.C. Publication 1181*, 1963, 296 pp.

2060. Thomas, J. J., Jr., E. M. Neptune, Jr. and H. C. Sudduth. Carbohydrate metabolism in rat brain under high oxygen pressure (HOP). *XXII Inter. Congr. physiol. Sci.*, Leiden. 1962, 2: Abstr. 354.

2061. Wood, J. D. and W. J. Watson. Gamma-amino butyric acid levels in the brain of rats exposed to oxygen at high pressure. *Canad. J. Biochem. Physiol.*, 1963, 41: 1907.

## 10. EFFECTS ON THE ENDOCRINE SYSTEM

Bean (2062) 1952, and Bean and Johnson (2067) 1952, exposed young adult albino rats, hypophysectomized and controls, repeatedly to oxygen at 70-90 pounds pressure for short periods (3 to 20 minutes) once or twice daily for several days or weeks. Carbon dioxide was continuously removed from the chamber using soda lime. The temperature was held at that approximately of the room and decompression was such as to avoid bubble formation. Although there was some individual variation, the data showed that hypophysectomy definitely delayed the onset and decreased the severity of the acute neuromuscular response and of the convulsive seizures induced by oxygen under high pressure (OHP). The severity of chronic motor paralysis, commonly induced by repeated exposure to OHP, was reduced or completely eliminated. Dyspnea was much less severe and the mortality diminished. Hypophysectomy provided marked protection against pulmonary damage by OHP. Lungs of control animals succumbing to OHP commonly showed severe damage, hemorrhage, congestion and a liver-like appearance in parts or all of the lung, which frequently sank in water; whereas those of hypophysectomized animals sacrificed under anesthesia were much less severely affected, some remaining entirely clear despite a much more rigorous exposure to OHP. Lowered metabolism may explain in part the delayed onset of acute neuromuscular reactions in the hypophysectomized animals, but their greater resistance to chronic effects of oxygen poisoning such as motor paralysis and lung damage, according to the authors, are not satisfactorily explained on this basis.

OHP if prolonged and repetitive causes certain cytological alterations of the adrenal cortex. Bean, Baker and Johnson (2065) 1953, found that single exposures of short duration to oxygen at 5.0 atmospheres induced very little change in the adrenals of rats. More prolonged and repetitive exposures caused distinct changes roughly paralleling the increased glandular weight, but considerable variation in the magnitude of the change was observed. The zona fasciculata was thickened, its constituent cells hypertrophied and its lipid content reduced. The adrenal cortices of those rats exhibiting residual paralyses were affected most, the outer portion of the zona fasciculata being completely devoid of large lipid droplets, although many fine sudanophilic bodies remained which probably were mitochondria. Lipid depletion and cell hypertrophy were present to a lesser degree in the zona reticularis. The zona glomerulosa was not significantly affected. The histological picture was characteristic of that induced by nonspecific stress and the procedure used did not reveal any change which might be considered peculiar to OHP administration. Bean (2063) 1955, has shown that hypophysectomy, rather than intensifying the adverse reaction to OHP, diminished the reaction. The number of reactions in hypophysectomized rats injected with ACTH was twice as great as those that were not injected, and about equal to those of unoperated control animals. Corticotropin and adrenal cortical hormones augment the pulmonary damage inflicted by OHP but are not essential to the precipitation of injury by oxygen. Adrenalin also enhances the toxic effect of OHP, particularly of pulmonary damage and of permanent motor disabilities, in both adrenalectomized and non-operated animals. Pulmonary edema and hemorrhage induced by OHP in the intact animal are to some degree of neurogenic origin, via the hypothalamus and sympathetico-adrenal system, including an increased secretion of adrenalin and nerve discharge to the thoracic viscera and to the lungs themselves. Sympathetic blocking agents afford some protection against OHP. The augmentation of the toxic effects of OHP by either endogenous or exogenous carbon dioxide is believed to be in large part of central origin, possibly within the hypothalamus. Any hormone that increases metabolism may augment



the toxic reaction via increased oxygen production. Increased metabolism induced by adrenalin may entail an increased utilization of cortical hormones and subsequent release of ACTH, etc. Adrenalin may also directly act on the hypothalamus and through the hypophyseal-adrenal system release increased quantities of adreno-cortical factors. Such hormones as thyroid and adrenalin may act directly on the vascular bed. Oxygen under high pressure increased capillary permeability with hemorrhage, congestion, edema and loss of proteins. Repeated exposure of young rats and baby chicks to OHP induces permanent motor disability, decreased growth, altered higher functions of the central nervous system and adversely affects the visual retina. These studies are also discussed by Bean, Johnson and Smith (2068) 1954. Gerschman and Fenn (2070) 1954, have found a decrease in the concentration of ascorbic acid in the adrenal glands of rats exposed to OHP, and this is taken as evidence that this type of stress may cause enhanced secretion of hormones from the adrenal cortex. Taylor has reported on effects of high oxygen on adrenalectomized, treated and untreated rats (2072) 1954. Two groups of rats (one unoperated, the other bilaterally adrenalectomized) were divided into subgroups and treated respectively with DOCA, cortisone (1 mg./100 gm. body wt.), thyroid (10 mg./100 gm. body wt. orally), adrenalin (single injection = 0.05 mg./rat subcutaneously) and adrenalin in combination with each of the other three substances, for seven days prior to exposure. Each of these groups also contained an untreated group. The animals were exposed for 14 days after operation to oxygen at 6.0 atmospheres and convulsion times were determined. The effect of adrenalectomy was significant (convulsion time 53 minutes as compared with 38.3 minutes,  $P < 0.0001$ ). In unoperated rats thyroid reduced the convulsion time ( $P < 0.01$ ) in agreement with previous work. This was not apparent in operated rats. The only other significant effect ( $P < 0.05$ ) was the interaction of cortisone with the operation; the convulsion time being reduced in unoperated and increased in operated animals. DOCA treated animals showed a rather low convulsion time and a severe degree of lung damage, and although the latter was not considered significant it was observed that a

deleterious effect might be concealed by the variability of the whole group. Thirty-two adrenalectomized rats were also exposed for 50 minutes. Those convulsing were rejected; the rest were divided into groups of seven with one being treated with DOCA and the other left untreated. On re-exposure there was no difference between the groups either in convulsion time or in the degree of lung damage.

2062. Bean, J. W. (The hypophysis as a determinant in the reaction of the mammal to oxygen at high pressure. *Amer. J. Physiol.*, 1952, 170: 508-517.

2063. Bean, J. W. Hormonal aspects of oxygen toxicity. pp. 13-19 in: *Proceedings of the underwater physiology symposium*. Edited by L. G. Goff, National Research Council, Washington, D.C. N.R.C. Publication 377, 1955, 153 pp.

2064. Bean, J. W. Tris buffer, CO<sub>2</sub>, and sympatho-adrenal system in reactions to O<sub>2</sub> at high pressure. *Amer. J. Physiol.*, 1961, 201: 737-739.

2065. Bean, J. W., B. L. Baker and P. Johnson. Cytological alterations of adrenal cortex induced by oxygen at high pressure. *Fed. Proc.*, 1953, 12: 11.

2066. Bean, J. W. and R. Bauer. Thyroid in pulmonary injury induced by O<sub>2</sub> in high concentration at atmospheric pressure. *Proc. Soc. exp. Biol., N.Y.*, 1952, 81: 693-694.

2067. Bean, J. W. and P. Johnson. Hypophyseal involvement in response to O<sub>2</sub> at high pressure. *Fed. Proc.*, 1952, 11: 9.

2068. Bean, J. W., P. Johnson and C. W. Smith. Adrenocortical and medullary factors in O<sub>2</sub> at high pressure. *Fed. Proc.*, 1954, 13: 9.

2069. Bean, J. W., P. Johnson, C. Smith and R. Bauer. Effects of thyroid and insulin on the pulmonary reaction to oxygen. *Fed. Proc.*, 1953, 12: 12.

2070. Gerschman, R. and W. O. Fenn. Ascorbic acid content of adrenal glands of rat in oxygen poisoning. *Amer. J. Physiol.*, 1954, 176: 6-8.

2071. Gerschman, R. and P. W. Nadig. Stress and oxygen poisoning. *Fed. Proc.*, 1953, 12: 50.

2072. Taylor, D. W. Effects of high oxygen on adrenalectomized, treated and untreated rats. *J. Physiol.*, 1954, 125: 46-47P.

2073. Taylor, D. W. Effects of adrenalectomy on oxygen poisoning in the rat. *J. Physiol.*, 1958, 140: 23-36.

## 11. EFFECTS OF BODY TEMPERATURE

It appears that lowering of body temperature has an effective action against high oxygen pressure toxicity and that this action is mostly because of reduced metabolic rate. This has been demonstrated by Popovic, Gerschman and Gilbert (2074) 1964, who exposed hibernating ground squirrels to 6.0 atmospheres of oxygen. These animals survived this condition for 18 hours. Hypothermic squirrels endured the con-

dition for six hours or more and euthermic animals endured it for only one-half hour. The oxygen consumption was respectively in the proportion of 1:12:40 (with survival times showing an inverse relationship as noted).

2074. Popovic, V., R. Gerschman and D. L. Gilbert. Effect of high oxygen pressure on ground squirrels in hypothermia and hibernation. *Amer. J. Physiol.*, 1964, 206: 49-50.

## 12. EFFECTS ON THE KIDNEYS

Rennie and Knox (2075) 1962, have observed, incidental to other studies, that oxygen breathing at high ambient pressures reduces renal blood flow but not glomerular filtration rate. The observations provide evidence for the dependency of renal oxygen consumption ( $V_{O_2}$ ) upon sodium reabsorption rather than upon renal blood flow.

2075. Rennie, D. W. and F. G. Knox. Renal blood flow,  $O_2$  consumption and sodium reabsorption during  $O_2$  breathing at high ambient pressure. *Physiologist*, 1962, 5: 200.

## 13. TOLERANCE

In general it is known that oxygen tolerance at rest at 60 feet exceeds the limits for "no decompression" diving at the same depth. No information is available regarding resting oxygen tolerance between a depth of 60 feet of sea water and sea level (where the oxygen tolerance of the central nervous system is known to be at least 24 hours). Exercise reduces the tolerance. Convulsions may be seen as early as 40 minutes at 35 feet. One of the great deficiencies of information in mixed gas or oxygen diving is the limit of oxygen tolerance while exercising at depths between 30 and 20 feet. Some information indicates that toxic effects do not occur at these depths with exposures as long as one and two hours respectively. There is as yet no indication whether oxygen toxicity can be produced at these pressures with normal levels of underwater activity (2090) 1956.

Taylor (2088) 1953, has pointed out that all who have studied the problem of oxygen toxicity agree that the metabolic condition of the experimental animal at the time of exposure bears importantly on the time of onset of toxic manifestations. In an experimental study of the effect of vitamin E deficiency on oxygen toxicity, Taylor

divided 28 rats into two groups each containing eight males and 6 females. Both groups were from the time of weaning given the same basic artificial diet with 20 percent casein and designed to contain negligible amounts of vitamin E. Animals in the first group were given in addition 5 mg. of alpha-tocopheryl acetate orally twice weekly. When nine months old all the rats were exposed to 5.0 atmospheres of oxygen (approximately 98 percent oxygen) for a standard period of 50 minutes during the whole of which they were under direct observation. In the first group convulsions were observed in only four animals while all 14 in the second group convulsed. In the first group only one animal died, but in the second group there was only one survivor. Both of these differences are highly significant ( $P < 0.01$  and  $0.001$  respectively). Autopsy was performed on all animals to assess lung damage which was arbitrarily classified into four degrees of severity. First impression seemed to indicate greater damage in the deficient animals, three of which showed damage of the most severe grade, as opposed to none in the control (second) group, but the overall differences were not significant. There was no macroscopic or microscopic liver damage. There seems to be no immediate fundamental explanation of these results other than such a postulate as enhanced toxicity from some abnormal metabolic formation or increase in normal cell metabolism in the absence of vitamin E (known to be a tissue anti-oxidant). Taylor has also studied the effects of methylene blue and glutathione on the manifestations of oxygen poisoning in vitamin E deficient rats (2089) 1958. As stated above, vitamin E deficient rats showed a decreased resistance to the effects of oxygen on the central nervous system when compared with rats treated with alpha-tocopherol acetate. Methylene blue and glutathione had smaller but definite protective effects. Lung damage was less in rats given alpha-tocopherol acetate or glutathione than in those given methylene blue or no supplement. Survival rates were high in rats maintained on alpha-tocopherol acetate and large doses of gamma tocopherol. All vitamin E deficient untreated rats exhibited hemolysis *in vivo* following exposure to abnormally high oxygen pressures. Tocopherol in any but the smallest doses gave



complete protection; glutathione gave some protection; methylene blue gave no protection (except in four animals exposed to pure oxygen at atmospheric pressure). Hemolysis was greater in the male than in the female animals.

In a study of the effect of various substances on the survival time of mice exposed to different high oxygen tensions, Gerschman, Gilbert and Caccamise (2081) 1958, exposed mice to various pressures of oxygen up to 10 atmospheres (at which level there was a minimum survival time of 19 minutes). Cystamine, reduced glutathione and thiourea had a detrimental effect at 1 or 1.5 atmospheres but protected mice at 6.0 atmospheres. Cystamine and oxidized glutathione did not protect at 1.0 atmosphere, but gave protection at 6.0 atmospheres of oxygen. DEDTC (diethyldithiocarbamic acid sodium salt) increased the survival time of mice in 6.0 atmospheres of oxygen. Trihydroxyphenone antioxidants showed some protective effect against oxygen toxicity in mice exposed to 6.0 atmospheres of oxygen. The results provided by these authors are not inconsistent with the notion of a possible common mechanism between oxygen poisoning and X-irradiation. The action of any given agent was found to depend upon the oxygen pressures to which the animals were exposed.

Gerschman, Gilbert, Nye and Fenn (2083) 1956, have studied the sensitivity of paramecium caudatum to oxygen toxicity as influenced by cobaltous and manganous ions and hematoporphyrin. Cobaltous chloride was protective at 5-20 atmospheres but injurious at 1-4 atmospheres; manganous chloride was protective at 9.0 atmospheres, but appeared detrimental at 2.0 atmospheres. Hematoporphyrin was detrimental at 9.0 atmospheres. These experiments emphasized the importance of studying the effects of given agents at different pressures of oxygen as well as at different intensities of radiation.

In a study of the anticonvulsant threshold of carbon dioxide in oxygen under high pressure, Chapin (2078) 1955, exposed 68 mice to 5.0 atmospheres of oxygen. All mice receiving only oxygen convulsed; all mice receiving less than 120 mm.  $P_{CO_2}$  in oxygen convulsed also. Fifty percent of the mice receiving 120 mm  $P_{CO_2}$  in oxygen convulsed and the rest died without convulsion. Only one out of 17 mice receiving more than

120 mm.  $P_{CO_2}$  convulsed. Mice receiving oxygen diluted with carbon dioxide convulsed sooner than mice receiving pure oxygen. The amount of shortening of convulsion time did not appear to be dependent upon the amount of carbon dioxide diluting the oxygen as long as the  $P_{CO_2}$  lay in the range of 27-120 mm. The tension at which carbon dioxide becomes anticonvulsant appears to be about 120 mm. (16 percent at 1 atmosphere).

Walker (2092) 1961, has also examined the question of involvement of carbon dioxide in the toxicity of oxygen at high pressure. He concluded that mice adapted to an atmosphere high in carbon dioxide (10-20 percent) are more resistant to the convulsive effects of oxygen at 6.0 atmospheres pressure than are untreated mice, but that long term adaptation to 20 percent carbon dioxide is in itself debilitating and negates the positive results. Increased tolerance may be essentially increased ability to withstand effects of carbon dioxide transport interference.

2076. Bean, J. W. (Reserpine and reaction to  $O_2$  at high pressure. *Fed. Proc.*, 1956, 15: 11.

2077. Cerchia, M. M. F., P. Mantegazzini and M. Parma. Epilessia iperossica e farmaci antiepilettici. *Ann. Med. Nav. Trop.*, 1956, 61: 244-253.

2078. Chapin, J. L. Anticonvulsant threshold of  $CO_2$  in oxygen under high pressure. *Proc. Soc. exp. Biol. N.Y.*, 1955, 90: 663-664.

2079. Galston, A. W. and S. M. Siegel. Antiperoxidative action of the cobaltous ion and its consequences for plant growth. *Science*, 1954, 120: 1070-1071.

2080. Gerschman, R. The biological effects of increased oxygen tension. pp. 171-179 in: *Man's dependence on the earthly atmosphere*. Edited by K. E. Schaefer. The MacMillan Company, New York, 1962, 416 pp.

2081. Gerschman, R., D. L. Gilbert and D. Caccamise. Effect of various substances on survival times of mice exposed to different high oxygen tension. *Amer. J. Physiol.*, 1958, 192: 563-571.

2082. Gerschman, R., D. L. Gilbert, S. W. Nye and W. O. Fenn. Role of anti-oxidants and of glutathione in oxygen poisoning. *Fed. Proc.*, 1955, 14: 56.

2083. Gerschman, R., D. L. Gilbert, S. W. Nye and W. O. Fenn. Sensitivity of paramecium caudatum to oxygen toxicity as influenced by cobaltous and manganous ions and hematoporphyrin. *Fed. Proc.*, 1956, 15: 72.

2084. Gilbert, D. L., R. Gerschman and W. O. Fenn. Effects of fasting and x-irradiation on oxygen poisoning in mice. *Amer. J. Physiol.*, 1955, 181: 272-274.

2085. Gottlieb, S. F. and R. B. Jagodzinski. Role of THAM in protecting mice against convulsive episodes caused by exposure to oxygen at high pressure. *Proc. Soc. exp. Biol., N.Y.*, 1963, 112: 427.

2086. Hempleman, H. V. Effect of pre-exposure to carbondioxide upon resistance to acute oxygen poisoning in the rat. *Gt. Brit. MRC, RNPRC, UPS. Rept. R.N.P. 56/860, U.P.S. 156*, March 1956, 5 pp.

2087. Kahn, H. E., Jr., C. E. Mengel, W. W. Smith and B. D. Hertton. Oxygen toxicity and vitamin E. *Aerospace Med.*, 1964, 35: 275.

2088. Taylor, D. W. Effects of vitamin E deficiency on oxygen toxicity in the rat. *J. Physiol.*, 1953, 121: 47P-48P.

2089. Taylor, D. W. Effects of tocopherols, methylene blue and glutathione on the manifestations of oxygen poisoning in vitamin E deficient rats. *J. Physiol.*, 1958, 140: 37-47.

2090. U.S. NRC. Oxygen. pp. 5-7 in: *Status of research in underwater physiology*. U.S. NRC-CUW, *Rept. 468*, March 1956, 24 pp.

2091. Van Den Brenk, H. A. and R. Moore. Effect of high oxygen pressure on the protective action of cystamine and 5-hydroxytryptamine in irradiated rats. *Nature Lond.*, 1959, 183: 1530-1531.

2092. Walker, I. G. The involvement of carbon dioxide in the toxicity of oxygen at high pressure. *Canad. J. Biochem. Physiol.*, 1961, 39: 1803-1809.

#### 14. EFFECTS ON PERFORMANCE

Frankenhaeuser, Graff-Lonnevig and Hesser (2093) 1960, tested four women and six men for psychomotor performance during exposure to oxygen at 3.0 atmospheres as compared to 1.0 atmosphere. The subjects had tasks including a visual choice reaction time (three colored light signals to which subjects respond by closing a switch); a visual simple reaction time (one light in response to which the subject closed one switch); and a mirror drawing (moving a stylus along a slit cut out in a metal plate creating a star). It was found that there was no systematic change in performance level, nor did the performance deteriorate when the time was increased to 30 minutes. The authors state that these tasks had proven to be an effective measurement in other experiments. Breathing pure oxygen at 3.0 atmospheres was considered safe up to two hours, but at 4.0 or more atmospheres the risk of convulsions increases rapidly. One subject did convulse after 17 minutes and yet there was no deterioration in performance prior to the seizure.

2093. Frankenhaeuser, M., V. Graff-Lonnevig and C. M. Hesser. (Psychomotor performance in man as affected by high oxygen pressure (3 atmospheres). *Acta physiol. scand.* 1960, 50: 1-7.

#### 15. PATHOLOGICAL EFFECTS

In laboratory animals severe pulmonary damage usually results from long exposure to oxygen under moderate pressure (Penrod (2098) 1956). The extent to which human lungs are damaged by similar exposures is not well known. There is reason to believe, in small animals at least, that lung damage and the central nervous system effects produced by oxygen under high pressures have separate etiologies. Evidence has been obtained that the principle factor involved in the pulmonary pathology is atelectasis which chiefly results from isolation of the areas due to excessive secretions in the small airways. The processes of atelectasis can be delayed or partially reversed by a number of procedures such as periodic positive pressure insufflation, intermittent exposure to an inert gas (such as nitrogen or helium), or by induced positive pressure breathing. Penrod has developed these points further (2099) 1956, where he has pointed out that when one bronchus is cannulated and the other is blocked prior to exposure of an animal to oxygen at high pressure, the obstructed portion of the lung shows massive congestion and complete atelectasis. The gross appearance is not unlike that usually seen in the lungs of laboratory animals exposed for long periods to oxygen at high pressure. They respond, however, as do lungs damaged by high oxygen pressure, to tracheal insufflation by dramatically regaining their original pink healthy color and consistency. The author presents reasons for believing that a major cause of the pulmonary damage produced by high oxygen pressures is simple atelectasis resulting from blockade of the smaller airways with resultant absorption of the gases peripheral to the obstruction; the process is reversible as can be shown by forcibly inflating the collapsed alveolar areas. The author further believes that the hormonal influences on pulmonary damage in high oxygen pressures are mediated through an influence on the patency of the distal airways. For further studies Penrod's paper (2101) 1958, should also be consulted. Jamieson and Van Den Brenk (2097) 1962, and Van Den Brenk and Jamieson (2103) 1962, have studied pulmonary damage in rats due to high pressure oxygen breathing. Changes in lung weights, histology



and bronchographic appearances are recorded in rats subjected to oxygen at 60 psi (gauge). Capillary congestion, progressing to alveolar exudation and hemorrhage was the earliest observable change. The results failed to support a postulate that lung damage due to oxygen poisoning is primarily an atelectasis due to bronchial obstruction. Positive pressure inflation of the lungs immediately *post mortem* did not reverse oxygen damage. Heparinization of rats was also without effect upon such damage. Exposure of lung tissue *in vitro* to 100 psi (gauge) of oxygen for five hours failed to cause changes similar to those observed for lungs exposed *in vivo* to oxygen under high pressure. Jamieson and Van Den Brenk used the Evans blue dye technique to determine increases in capillary permeability in the lungs of rats subjected to pure oxygen under pressure at 60 psi (gauge). Considerable leakage of plasma during OHP was found. Hemoglobin in lung tissue was also increased remarkably during OHP. Zagorskii (2105) 1960, produced oxygen intoxication in five adult cats and dogs by breathing oxygen under a higher than ambient pressure. Histological analysis of the nervous system showed most pronounced changes in the cerebellum, in the optic thalami and in the caudal spinal cord sections. There were marked peripheral changes in the sensory neurones of the spinal and cranial sensory ganglia. The character of these changes supported the hypothesis that tissue hypoxia caused by the angiospastic action of increased partial pressure of oxygen in the blood is one cause of oxygen poisoning. A study by Edström and Röckert (2095) 1962, exposed rats to oxygen at 6.0 atmospheres daily for about eight weeks in one series and for about four weeks in a second series. The exposure times were so adapted as to give a low incidence of convulsions and lung symptoms. The animals did not show any evidence of lung damage at autopsy. Slight motor symptoms of a paralytic nature developed in some rats of the first series after about two weeks. Symptoms regressed during continuation of treatment and had disappeared after five weeks. Histological investigation of the nervous system after seven to nine weeks showed no degeneration. Rats of the second series showed no neurogenic symptoms. Histologically there was an increase in the size of

the nucleolus of neurons of the stellate ganglion and of the adrenal medulla. In both series there was a decrease in the weight with thickening of the zona fasciculata.

Pathological processes have been summarized by Lambertsen (*Fundamentals of Hyperbaric Medicine*, Publication No. 1298, National Academy of Sciences, National Research Council, Washington, D.C., 1966, page 29). He points out that no specific measures are known to provide a rational basis for treating cells damaged by the toxic processes. Given severe central nervous system effects and sustained convulsive or neurological damage, these sequelae should be managed as other forms of convulsion or central nervous system injury. Until more extensive study of the general pathology of the central nervous system oxygen toxicity has been carried out recommendations for other than supportive treatment are not likely to be significant. Lambertsen also calls attention to damage of the lungs leading to diffuse atelectasis, pulmonary edema and bronchial pneumonia. Because death results from failure of pulmonary gas exchange such measures as artificial respiration and prophylactic use of antibiotics are only of aid to the less seriously injured individual. In selecting the gas for lung ventilation, a concentration of oxygen not exceeding 60 percent at sea level is the gas of choice (because higher tensions of oxygen might presumably aggravate the existing pulmonary condition). Should the lungs of a patient have been so severely affected by pulmonary oxygen poisoning that an anoxemia develops, even at inspired oxygen pressures of several atmospheres, a quandary will exist that will certainly end only with the death of the patient. Treatment by lowering the oxygen pressure will result in further anoxemia; treatment of anoxemia with oxygen at normal or higher pressures will result in further damage. Thus if such mechanical approaches of the use of the heart-lung machine for extrapulmonary oxygenation are ignored as being impractical, no approach to the reversal of severe pulmonary damage appears feasible at this time. On this basis the pulmonary limits of oxygen tolerance deserve the most serious attention in therapy with high oxygen pressures, as Lambertsen has pointed out.

2094. Beehler, C. C., N. L. Newman, J. F. Culver and T. J. Tredici. Retinal detachment in adult dogs resulting from oxygen toxicity. *Arch. Ophthalm.*, 1964, 71: 665.

2095. Edstrom, J. E. and H. Rockert. The effect of oxygen at high pressure on the histology of the central nervous system and sympathetic and endocrine cells. *Acta physiol. scand.*, 1962, 55: 255-263.

2096. Jamieson, D., K. Ladner and H. A. S. Van Den Brenk. Pulmonary damage due to high pressure oxygen breathing in rats. *Aust. J. exp. Biol. med. Sci.*, 1963, 41: 491.

2097. Jamieson, D. and H. A. S. Van Den Brenk. Pulmonary damage due to high pressure oxygen breathing in rats. 3. Quantitative analysis of fluid changes in rat lungs. *Aust. J. exp. Biol. med. Sci.*, 1962, 40: 309-314.

2098. Penrod, K. E. Pulmonary damage in high oxygen pressure. *Fed. Proc.*, 1956, 15: 143.

2099. Penrod, K. E. Nature of pulmonary damage produced by high oxygen pressures. *J. appl. Physiol.*, 1956, 9: 1-4.

2100. Penrod, K. E. Factors in oxygen high pressure pulmonary damage. *Fed. Proc.*, 1957, 16: 100.

2101. Penrod, K. E. Lung damage by oxygen using differential catheterization. *Fed. Proc.*, 1958, 17: 123.

2102. Sapov, I. A. O mekhanizme toksicheskogo deistviia kisloroda na legochnuiu tkan'. [On the mechanism of the toxic effect of oxygen on pulmonary tissue.] *Bull. Biol. Med. exp. URSS*, 1953, 4: 40-45.

2103. Van Den Brenk, H. A. S. and D. Jamieson. Pulmonary damage due to high pressure oxygen breathing in rats. 1. Lung weight, histological and radiological studies. *Aust. J. exp. Biol. med. Sci.*, 1962, 40: 37-49.

2104. Van Den Brenk, H. A. S. and D. Jamieson. Potentiation by anesthetics of brain damage due to breathing high pressure oxygen in mammals. *Nature, Lond.*, 1962, 194: 777.

2105. Zagorskii, IU. M. O morfologicheskikh izmeneniakh tsentral'noi i nekotorykh otdelov perifericheskoi nervnoi sistemy zhivotnykh pri giperoksemii. [Morphological changes in the central nervous system and certain parts of the peripheral nervous system in hyperoxemic animals.] *Arkh. Pat.*, 1960, 22: 27-34.

## 16. TREATMENT: GENERAL STUDIES

The general references on treatment included in this section will not be discussed in detail since the subject has been covered by Lanphier and Brown (*Fundamentals of Hyperbaric Medicine*, Publication No. 1298, National Academy of Sciences, National Research Council, Washington, D.C., 1966, page 33 *et seq.*). In so far as military medicine is concerned oxygen under high pressure has a therapeutic value primarily in the treatment of carbon monoxide poisoning and possibly in the management of air embolism to shorten the time at which the victim must be

repressurized. Lanphier and Brown have pointed out that the physiological effects of high pressure, like those of most abnormal environments, are primarily detrimental to man. To use these effects for therapeutic advantage means keeping the desired action within certain suitable limits while avoiding harm from simultaneous effects. They have made it clear that our present knowledge concerning the physiology of high pressure is not complete; however, utilizing what is known can do much towards placing clinical applications of this procedure on a logical and reasonably safe basis. The area of most recent interest in high pressure therapy deals with elevation of inspiratory oxygen partial pressure as a method of overcoming or eliminating various types of hypoxia. Although the laws of Dalton and Henry supply the physical basis for this application, they do not go far by themselves toward providing a reasonable physiological rationale. Lanphier and Brown have made it clear that it is neither accurate or useful to suggest that elevating the inspiratory oxygen pressure by a factor of 15 will indeed elevate oxygen pressures by the same factor throughout the body. The picture is complicated by the properties of hemoglobin, by oxygen uptake and blood flow and by uncertainties concerning the diffusion of oxygen from capillaries into the tissue, quite apart from the imperfect knowledge of the pathological physiology of the diseased states being treated. Clinical and experimental studies of strictly controlled design must be conducted before practical indications for hyperbaric therapy can be truly defined. Several perplexities and false hopes have arisen purely from failure to apply physiological knowledge presently available. At this juncture perhaps even more important analysis of the problem in terms of such knowledge aids in defining the true areas of uncertainty and offers suggestions for critical experiments to cast light upon them. Answers to a certain number of fundamental questions will go far in enhancing our comprehension and our ability to make useful predictions according to Lanphier and Brown. These authors go further to say that the understanding of the potential benefits and limitations of oxygen administered under high pressure is best sought by considering the stages in the process of oxygen transfer, the disordered condi-



tions in each that can result in hypoxia and the therapeutic effects that increased oxygen pressure may cause.

Lanphier and Brown have offered certain conclusions of a tentative nature which may be generally related to proposed therapeutic applications. They state that hypoxia of pulmonary origin ought to seldom require treatment with oxygen under high pressure. However, this application provides a quite unique means of handling hypoxia caused by continued blood flow through unventilated alveoli. In this application, however, the tendency of oxygen to produce atelectasis and overt lung damage may cause a worsening of the basic pathological process. Since oxygen under high pressure is capable of increasing the oxygen capacity of the blood the technique may be applicable for any condition in which hemoglobin is inactivated or lost. The ability to increase the oxygen content of oxygenated blood provides the only method known of offsetting massive venous admixture to obtain normal or near-normal arterial values. Nevertheless the presence of a large right-to-left shunt largely eliminates the feasibility of elevating arterial oxygen to supranormal levels. Maintaining significantly higher arterial oxygen content does provide an effective way of compensating for diminished blood flow in otherwise normal vascular beds. This suggests firm indications for oxygen at high pressure as a therapeutic method in shock and in peripheral vascular trauma or disease. Nevertheless our present defects of knowledge as to the critical levels of tissue  $P_{O_2}$  and the relation to capillary blood  $P_{O_2}$  prevents prediction of the decrement of blood flow that can be compensated at practical levels of oxygen under high pressure. Lanphier and Brown also point out that hyperbaric oxygenation offers relatively little in extending the duration of tissue function or survival in temporary complete blood flow cessation. Gains can be enhanced by combining oxygen under high pressure and hypothermia, but may still remain short of earlier optimistic predictions. They point out further that oxygen under high pressure extends the distance of effective oxygen diffusion, but this is to such a limited extent that it is not capable of handling large regions of ischemia. The value of the method in treating myocardial in-

farction, for example, may best be negligible unless there is sufficient collateral circulation remaining or unless effects on the margin of the affected region are significant, for example in reducing the likelihood of ventricular fibrillation. Oxygen under high pressure may be of value in stroke only in those forms involving a critical reduction of blood flow without actual obstruction of end arteries. If there is obstruction of a relatively small proportion of the capillaries in a particular vascular bed, or with limited increases in the diffusion pathway of oxygen as in tissue edema, Lanphier and Brown feel that oxygen under high pressure may be of distinct value. In combination with hypothermia oxygen under high pressure may be of increasing value if reduction of blood flow with hypothermia is obviated. The capacity of oxygen under high pressure to increase tissue  $P_{O_2}$  for such purposes as radiation therapy and for the treatment of anaerobic infections may be greatly variable depending in each instance upon the extent of remaining local blood flow and on the oxygen uptake of tissues in the pathway of the diffusion. Finally these authors assert that the levels of oxygen under high pressure requisite for significant benefit are such that the oxygen toxicity may severely limit the safe time duration of treatment. Therefore, the clearest indications of possible benefit are in those conditions where the requirement for oxygen under high pressure is of short duration and where the basic pathological process can be therapeutically reversed or blocked during a given exposure. In conditions of longer duration, the value of oxygen under high pressure depends to a great extent upon the possible persistence of its beneficial effects in intervals between relatively brief periods of repeated treatment exposure.

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#### 17. TREATMENT: VASCULAR SHOCK

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#### 18. PRESSURE OXYGENATED SOLUTIONS

A basic limitation of oxygen use in diving is the supervention of convulsions and other toxic effects of oxygen when certain depths are exceeded. For this reason, the policy has been to keep the oxygen partial pressure below 1.6 atmospheres by dilution with inert gases. As depth is increased the oxygen percentage must be diminished to maintain non-toxic inspiratory mixtures. This precise control of oxygen percentage is technically difficult at great depths. In this connection experimental studies of fluid breathing have attracted a certain recent interest. These studies have not been extended to man.

From the references given in this section two may be selected for special discussion. Kylstra and Lanphier (2196) 1964, ventilated anesthetized dogs mechanically with bubble-oxygenated saline for 50 minutes in a chamber pressurized with air at 3.0 atmospheres absolute. With fluid ventilation at rates of 4200 ml./minute and with an inspiratory P<sub>O<sub>2</sub></sub> below 2200 mm. Hg, the arterial oxygen content ranged from 14.7 to 21.6 volume percent at rates of oxygen uptake up to 120 ml./minute in three dogs. The total computed dead space for oxygen was less than 287 ml. Gas exchange during fluid breathing of mammals may be impaired as a result of subnormal ventilation due to high airway resistance to fluid flow, poor mixing and slow gas diffusion in fluid-filled alveoli and uneven distribution of inspired fluid. Of these factors, ventilation appears to be the most critical. Marked respiratory insufficiency and death followed reversion to gas breathing. One dog survived seven days after having been ventilated with fluid for one hour. Pressure-volume diagrams obtained during inflation of the lungs with air after 50 minutes of fluid ventilation suggest marked increases in alveolar surface tension. Pegg, Horner and Wahrenbrock (2198) 1963, pointed out that since the solution of a gas in a liquid is directly



proportional to the applied partial pressure, it is possible with sufficient pressure to dissolve physically an arbitrarily great amount of oxygen in a liquid. Saline at 37°C. exposed to oxygen at 10 atmospheres absolute will contain in solution 20 volumes percent of oxygen. In the authors' experiments 30 etherized and tracheotomized rats were tied in lucite frames and placed in a pressure chamber breathing an oxygenated saline solution. On immersion the heart rate dropped, the irregularity of respiration during the first three minutes gave way to a respiratory rate of 28 per minute (compared with a control rate of 69 per minute). As the pressure increased the survival time increased. Thus, at 2.5 atmospheres the survival time was approximately five minutes; this rose to 170 and 248 minutes at 10 atmospheres and dropped to 90 and 135 minutes at 20 atmospheres. After 30 minutes the rats were decompressed and the lungs drained. Eight rats resumed normal breathing, in some, however, in 15 minutes there was a serosanguinous fluid bubbling from the end of the tracheal tube. Respiration was slow and labored; the animals became cyanotic and some died even though 100 percent gaseous oxygen was administered.

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## VII. NOXIOUS AGENTS

### A. CARBON MONOXIDE

#### 1. GENERAL STUDIES OF CARBON MONOXIDE POISONING

The literature on carbon monoxide is large, and therefore a selection has had to be made

of those reports to be considered in this volume. Moreover, the knowledge regarding carbon monoxide has not changed drastically in the last ten years and therefore reference can be made to the sections on carbon monoxide in volumes I and II of this Sourcebook.

The reader is particularly referred to a U.S. NRC report on the *Status of research in underwater physiology* (2204) 1956, in which the toxicity of carbon monoxide is compared at sea level and at depth. At sea level the toxicity of carbon monoxide is proportional to the amount of COHb formed, while at depth a diver may tolerate considerably higher ratios of COHb because some of the oxygen transport requirements are met by oxygen in solution (due to the increased partial pressure of oxygen at depth). However, since the reconversion of COHb to oxyhemoglobin is slow he may be in immediate difficulty on ascent.

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#### 2. CARBON MONOXIDE IN SUBMARINES AND OTHER NAVAL VESSELS

Contamination of the atmosphere is still a potential problem in fleet type submarines where diesel engines are used for propulsion. In such vessels operating under strong following winds engine exhaust gases may not be carried away completely from air intake. The advent of the nuclear powered submarines has greatly reduced the contamination of the submarine atmosphere by carbon monoxide. A case of mass carbon

monoxide poisoning in a submarine has been reported by Alvis and Tanner (2206) 1952. Men engaged in active work were affected first. Headache was the first symptom noted, and all aboard were affected except one. There was nausea and vomiting, as well as headache, and the headache was so severe that sedation was required. The carbon monoxide concentration in the air was found to be 0.01 percent; the carbon dioxide level was at 2 percent. Exposure lasted for approximately 10 hours. It was suggested that the high carbon dioxide percent did not cause the condition but tended to hasten the onset of carbon monoxide poisoning symptoms. All aboard probably had carboxyhemoglobin saturations between 10 and 20 percent; several between 20 and 30 percent, and a few may have had as high as 30 to 40 percent saturation. As these authors have reported elsewhere (2207) 1952, this episode illustrates the danger of such a situation developing aboard snorkel equipped submarines under diesel power. The influence of work and an elevated concentration of carbon dioxide in the atmosphere in precipitating the toxic symptoms of carbon monoxide poisoning are demonstrated in this incident. The reader is referred to a statement on acceptable limits of concentrations of carbon monoxide in submarines (Gt. Brit. MRC., 2209). The maximum permissible level of carbon monoxide in nuclear powered submarines is given as 0.005 percent (50 parts per million). The following table gives maximum times allowable for given exposures:

Percent	pp 10,000	ppm	Maximum times of exposure
0.005	0.5	50	indefinite
0.01	1	100	6 hours
0.02	2	200	3 hours
0.04	4	400	1½ hours
0.05	5	500	1 hour
0.10	10	1000	½ hour
0.20	20	2000	¼ hour

Carbon monoxide as a habitability factor in prolonged submarine submergence has been studied by Nichols and Kinsey (2210) 1953. During routine analysis of the air of the submarine USS Haddock which was used for *Operation Hideout* (the purpose of which was to ascertain the effect of prolonged exposure to low

concentrations of carbon dioxide) a significant concentration of carbon monoxide was also found. Further testing was done to determine the rate of accumulation and diurnal variation, if any. Concentrations varying between 50 ppm and 100 ppm were present for a period of 12 days, and concentrations in excess of 100 ppm for a period of 4 days. At this point, hopcalite canisters were installed in the ventilation system and the carbon monoxide concentration was reduced considerably. Carbon monoxide blood saturation in men tested dropped rapidly upon return to outboard ventilation. However, the rate of elimination appeared slower than reported by other workers, since after 12 hours on weather air, significant saturations were still present. It was established that unrestricted smoking in a sealed space, such as a submarine during prolonged submergence, can give rise to toxic concentrations of carbon monoxide. Contamination of intake air from any source of exhaust gas can cause a carbon monoxide buildup (2212, 1956). In certain types of oil lubricated high pressure compressors cylinder temperatures may become high enough to promote partial combustion of the oil. Careful attention to the type of compression and maintenance must be given to keep the carbon monoxide within allowable concentrations.

2206. Alvis, H. J. and C. W. Tanner. Carbon monoxide toxicity in submarine operations. Report of a case. *Arch. industr. Hyg.*, 1952, 6: 404-406.

2207. Alvis, H. J. and C. W. Tanner. Carbon monoxide toxicity in submarine medicine, a case report. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 002 015.03, Rept. no. 8*, 1952.

2208. Bogatkov, P. I., Iu. G. Nefedov and M. I. Poletaev. Vydikhaemyi vozdukh kak istochnik zagriazneniia okis'iu ugleroda vozdukhnoi sredy germetichnykh pomeshchenii. [Expired air as a source of carbon monoxide contamination of the air environment of hermetically sealed compartments.] *Vo.-med. Zh.*, 1961, 2: 37-39.

2209. Gt. Brit. MRC. Statement on acceptable levels of concentrations of carbon monoxide in submarines. Gt. Brit. MRC, RNPRC, SMS. *Rept. S.M.S. 23*, 2 pp.

2210. Nichols, G., Jr. and J. L. Kinsey. Carbon monoxide as a habitability factor in prolonged submarine submergence. U.S. Navy. Submarine Base, New London. Conn. Medical research laboratory. *Project NM 002 015.10.01, Rept. no. 223*, 16 April 1953, 10 pp.

2211. Soegård, H. Risikoen for kulilteforgiftning i militære motorvogne. Risks of carbon monoxide poisoning in military vehicles. *Militærlaegen*, 1960, 66: 55-60.



2212. U.S. Navy. Carbon monoxide poisoning. pp. 173-175 in: *Submarine medicine practice*. U.S. Navy, BuMed, NAVMED—P 5054, Gov't. Printing Office, Washington, D.C., 1956, 357 pp.

### 3. CLINICAL PICTURE, FUNCTIONAL CHANGES AND PATHOLOGICAL EFFECTS

As in previous years, carbon monoxide persists as a potential hazard in industry and in caisson operations, as well as in submarine and diving. After prolonged moderate exposure to carbon monoxide there may be symptoms of acute intoxication or the symptoms of chronic carbon monoxide poisoning may indeed develop without any preceding symptoms of acute intoxication. There may be headache, lassitude and drowsiness, insomnia, irritability, memory loss, vertigo, tremor and slight confusion. With blood saturations from 10 to 20 percent there may be slight headache. Saturations of 20 to 30 percent may be associated with throbbing headaches, while saturations of 30 to 40 percent may be associated with weakness, dizziness, dimness of vision, nausea and vomiting. At saturations of 40 to 50 percent there may be collapse or syncope with acceleration of respiratory and pulse rates. Cheyne-Stokes respiration may supervene at 50 to 60 percent saturation and there may be coma with intermittent convulsions. Death may occur at saturations between 60 and 80 percent. Attention may also be called to such symptoms as palpitation, precordial pain, dyspnea, colic, attacks of diarrhea, polyuria, impotence and reduced tolerance for alcohol. There may also be attacks of elevated temperature and disturbances of vision and hearing. Circulatory responses of normal and carbon monoxide acclimatized dogs during carbon monoxide inhalation have been reported by Lillehei, Wilks and Carter (2220) 1954. During inhalation of 0.5 percent carbon monoxide in air for at least 30 minutes (sufficient to produce over 50 percent carboxyhemoglobin) normal and nembutal anesthetized dogs showed: 1) a rise in pulse rate, respiratory rate, mean pulmonary arterial pressure and cardiac output; 2) a relatively smaller rise in mean intrapleural pressure; and 3) little or no change in mean femoral arterial and left atrial pressure. Dogs which had been gradually acclimatized to breathing 0.1 percent carbon

monoxide in air for six to eight hours daily over a period of a year were found to have a significantly lower pulse and respiratory rate, a higher mean pulmonary arterial pressure, but approximately the same mean femoral arterial and intrapleural pressure as normal dogs. Wagemann (2230) 1960, has pointed out that in acute carbon monoxide intoxication the cochlear and/or vestibular apparatus are damaged. It is stated that the vestibular disturbances are central in type and that they generally recover. The recovery of the damaged hearing on the other hand is less certain. Courville (2214) 1957, has called attention to demyelination as a delayed residual of carbon monoxide asphyxia. According to Dutra (2215) 1952, the cerebral lesions occurring as a residue of carbon monoxide poisoning consist essentially of dilatation of blood vessels, edema, perivascular hemorrhages, degeneration and death of ganglionic cells, focal demyelination and foci of necrosis. Each of these is either directly or indirectly caused by a reduction of the supply of oxygen to the brain.

Garassini and De Santis (2216) 1960, have described a case of a 49 year old man who suffered acute carbon monoxide poisoning from a wood burning stove who presented typical acute symptoms of deep coma, cyanosis of the face and extremities and shallow and rapid respiration and pulse upon arrival at the hospital. After emergence from the coma the patient displayed, in addition to pyramidal symptoms, neuritis of the right brachial plexus followed by muscular atrophy of the regions involved. No cause for this, other than the carbon monoxide poisoning, could be found. The symptoms relating to the brachial plexus improved progressively. Schwarz and Müller (2226) 1960, reported the case of a 21 year old woman suffering from severe carbon monoxide poisoning with psycho-pathologic manifestations, including disturbance of consciousness, confusion and amnesia. Five months later there were epileptic attacks which continued for three years. The epileptic sequelae were considered by the authors to be related to the original carbon monoxide poisoning. For EEG changes in carbon monoxide poisoning, reference may be made to papers by Lennox and Petersen (2219) 1958, and Takahashi (2228) 1961. Electrocardiographic changes have

been described by Bouvrain, Gaultier, Gervais and Pasquier (2213) 1960.

2213. Bouvrain, Y., M. Gaultier, P. Gervais and P. Pasquier. (Les accidents cardiaques retardés de l'oxyde de carbone. *Sem. Hop. Paris*, 1960, 36: 3163-3172.

2214. Courville, C. B. The process of demyelination in the central nervous system. IV. Demyelination as a delayed residual of carbon monoxide asphyxia. *J. nerv. ment. Dis.*, 1957, 125: 534-546.

2215. Dutra, F. R. Cerebral residua of acute carbon monoxide poisoning. *Amer. J. clin. Path.*, 1952, 22: 925-935.

2216. Garassini, G. and G. De Santis. Interessamento del sistema nervoso nell'ossicarbonismo acuto: contributo clinico. Un caso di paresi del plesso brachiale destro. *Folia med., Napoli*, 1960, 43: 1048-1054.

2217. Herbich, F. and A. Stacher. Zur chronischen Kohlenmonoxydeinwirkung auf das Knochenmark. *Wien. Z. inn. Med.*, 1961, 42: 338-340.

2218. Lambertsen, C. J. Harmful effects of oxygen, nitrogen, carbon dioxide, and carbon monoxide. Carbon monoxide. pp. 716-719 in: *Medical physiology*. Edited by P. Bard, C. V. Mosby Company, St. Louis, 1961, 1339 pp.

2219. Lennox, M. A. and P. B. Petersen. Electroencephalographic findings in acute carbon monoxide poisoning. *EEG clin. Neurophysiol.*, 1958, 10: 63-68.

2220. Lillehei, J. P., S. S. Wilks and E. T. Carter. Circulatory responses of normal and of CO-acclimatized dogs during CO inhalation. *Fed. Proc.*, 1954, 13: 89.

2221. Middleton, G. D., D. W. Ashby and F. Clark. Delayed and long-lasting electrocardiographic changes in carbon-monoxide poisoning. *Lancet*, 1961, 1: 12-14.

2222. Musselman, N. P., W. A. Groff, P. P. Yevich, F. T. Wilinski, M. H. Weeks and F. W. Oberst. Continuous exposure of laboratory animals to low concentration of carbon monoxide. *Aerospace Med.*, 1959, 30: 524-529.

2223. Paeslack, van V. Diabetes mellitus nach Kohlenoxydvergiftung. *Schweiz. med. Wschr.*, 1961, 91: 946-949.

2224. Rapoport, K. M. O deistvii povyshennogo davleniia kisloroda pri eksperimental'noi gipolsemii, vyzvannoi otravleniem okis'iu ugleroda. [The effect of increased partial hypoxemia induced by carbon monoxide poisoning.] *Patol. Fiziol. Eksp., Ter.*, 1959, 3: 27-32.

2225. Schollmeyer, von W. and M. Dises. Zur Diagnose chronischer und subakuter CO-Vergiftung. *Dtsch. Gesundheitswes.*, 1961, 16: 1403-1407.

2226. Schwarz, von B. and D. Müller. Symptomatische Epilepsie nach Kohlenoxydvergiftung. *Z. ges. inn. Med.*, 1960, 15: 1104-1112.

2227. Schwedenberg, T. H. Leukoencephalopathy following carbon monoxide asphyxia. *J. Neuropath.*, 1959, 18: 597-608.

2228. Takahashi, K. Cardiac disturbances due to CO poisoning in experimental animals. I. Electrocardiographic changes due to CO poisoning and those under the influences of fluid infusion. *Tohoku J. exp. Med.*, 1961, 74: 211-223.

2229. Takahashi, K. Cardiac disturbances due to CO poisoning in experimental animals. II. Changes of the heart excitability due to acute CO poisoning. *Tohoku J. exp. Med.*, 1961, 74: 225-233.

2230. Wagemann, W. Das otologische Bild der Kohlenoxydvergiftung. *Z. Laryng. Rhinol.*, 1960, 39: 691-702.

2231. Wieland, H. Die Beeinflussung der Herzstromkurve durch Kohlenoxyd. *Arztl. Forsch.*, 1955, 9: 78-87.

2232. Wilks, S. S. Effects of pure carbon monoxide gas injection into the peritoneal cavity of dogs. *J. appl. Physiol.*, 1959, 14: 311-312.

2233. Wilks, S. S. and R. T. Clark, Jr. Carbon monoxide determinations in post-mortem tissues as an aid in determining physiologic status prior to death. *J. appl. Physiol.*, 1959, 14: 313-320.

2234. Wilks, S. S., J. F. Tomashefski and R. T. Clark, Jr. Physiological effects of chronic exposure to carbon monoxide. *J. appl. Physiol.*, 1959, 14: 305-310.

#### 4. MECHANISMS OF CARBON MONOXIDE POISONING

Interference with oxygen transport mechanisms in the blood is still regarded as the major action of carbon monoxide on the body. It has also been pointed out that carbon monoxide has an affinity for respiratory enzymes but this point is mainly of theoretical concern. Thus Breckenridge (2236) 1953, has reported on carbon monoxide oxidation by cytochrome oxidase in muscle; and Fati, Molé and Pecora (2238) 1960, have shown that daily carbon monoxide poisoning for three days in rabbits produced a progressive reduction in erythrocytic phosphoglucomutase activity which persisted ten days or longer after the poisoning. This inhibition, according to the authors, must be considered as independent of the oxygen deficiency produced by the poisoning, for in control animals kept in an atmosphere of nitrogen until the appearance of symptoms of asphyxia, no appreciable change in phosphoglucomutase activity appeared. The reader is referred to a paper on the effect of carbon monoxide poisoning in rabbits upon oxygen consumption and respiratory rate and respiration time in the erythrocytes (Molé (2242) 1960). The author concluded that carbon monoxide acts upon the oxygen consumption of the erythrocytes by slowing down aerobic oxidation without reducing the total value.

2235. Ackerman, E. and R. L. Berger. Reaction of oxyhemoglobin with carbon monoxide. *Biophys. J.*, 1963, 3: 493-505.



2236. Breckenridge, B. Carbon monoxide oxidation by cytochrome oxidase in muscle. *Amer. J. Physiol.*, 1953, 173: 61-69.

2237. Candura, F., A. Craveri and F. Brasca. La fibrinolisi nell'ossicarbonismo acuto. *Ricerche sperimentali. Folia med., Napoli*, 1961, 44: 400-408.

2238. Fati, S., R. Molé and L. Pecora. Gli enzimi glicolitici del globulo rosso nell'intossicazione ossicarbonica. Nota III. Il comportamento della fosfoglicomutasi eritrocitaria nell'ossicarbonismo acuto. *Folia med., Napoli*, 1960, 43: 1092-1097.

2239. Gibson, Q. H. Some observations on the reactions of two annelid haemoglobins with oxygen and with carbon monoxide. *Proc. roy. Soc.*, 1955, 143: 334-342.

2240. Gibson, Q. H. The direct determination of the velocity constant of the reaction  $\text{Hb}_4(\text{CO})_3 + \text{CO} \rightleftharpoons \text{Hb}_4(\text{CO})_4$ . *J. Physiol.*, 1956, 134: 123-134.

2241. Gwózdź, B., F. M. Spióch and J. S. Dutkiewicz. Untersuchungen über den Einfluss des Cytochroms C auf die Gewebeatmung von mit Kohlenoxyd vergifteten Tieren. *Z. Vitam.- Horm.- u. Fermentforsch.*, 1961, 11: 282-289.

2242. Molé, R. Il consumo di ossigeno degli eritrociti di conigli intossicati acutamente con CO. *Boll. Soc. ital. Biol. sper.*, 1960, 36: 973-975.

2243. Sendroy, J., Jr. and J. D. O'Neal. Relative affinity constant for carbon monoxide and oxygen in blood. *Fed. Proc.*, 1955, 14: 137.

## 5. UPTAKE AND ELIMINATION OF CARBON MONOXIDE

The uptake of carbon monoxide depends first of all upon the absorption of the gas by the lungs. This has been investigated by Forster, Fowler, Bates and VanLingen (2249) 1954, who have studied the absorption of carbon monoxide by the lungs during breathholding in seven normal subjects. The alveolar carbon monoxide concentration did not fall exponentially with time as had been assumed by previous workers. The most likely explanation of this phenomenon is that the diffusing capacity per unit gas volume varies throughout the lung. The rate of uptake of carbon monoxide by the normal human erythrocyte and experimentally produced spherocytes has been reported by Carlsen and Comroe (2247) 1958. The uptake of the gas by the erythrocyte involves first of all diffusion across the cellular membrane, secondly intraerythrocytic diffusion, and finally chemical combination with hemoglobin. The experiments suggest that surface area and maximum linear distance for intracellular diffusion do not measurably retard gas uptake. Shrunken erythrocytes showed a marked decrease in the rate

of gas uptake and it is hypothesized that in the shrunken cells a change in the orientation and concentration of intraerythrocytic hemoglobin and/or of the membrane components may have impeded gas diffusion. For photocolometric determinations of rate of uptake of carbon monoxide by human red cell suspensions at 37°C. a paper by Forster, Roughton, Kreuzer and Briscoe (2251) 1952, should be consulted, as should also a study by French and Hall (2252) 1954, on the time course of carboxyhemoglobin formation in subjects exposed to carbon monoxide for periods of ten to sixteen hours, and its modification by intermittent breathing of 100 percent oxygen. Joels and Pugh (2254) 1958, have developed carbon monoxide dissociation curves of human blood which differ slightly from the curves published in 1912 by Douglas and colleagues. The effect of levels of exercise upon pulmonary diffusing capacity by steady-state methods using oxygen and carbon monoxide in normal subjects has been reported by Shepard, Martin, White, Permutt, Varnauskas and Riley (2258) 1958. Three normal young men carried out different levels of treadmill exercise with and without hypoxia. Subjects were studied at each of four levels of exercise producing oxygen uptake between one and two-and-half liters per minute and cardiac outputs between nine and 22 liters per minute. Diffusing capacity for carbon monoxide increased progressively with increasing exercise in all subjects. It was higher during hypoxia than during air-breathing at the same level of exercise, as were total ventilation, tidal volume and cardiac output. It appears that this increase in the diffusing capacity for carbon monoxide cannot be explained solely on the basis of increased affinity of hemoglobin for carbon monoxide during hypoxia. Diffusing capacity for oxygen did not increase significantly with increasing exercise after cardiac output had reached 15 liters per minute. These data support the belief, based on theoretical considerations that the steady-state diffusing constant for oxygen and steady diffusion constant for carbon monoxide are not related in the same way to the diffusing capacity of the lungs.

2244. Borbély, F. Über die Existenz der chronischen Kohlenoxydvergiftung. *Internist*, 1961, 2: 265-269.

2245. Burrow, B., A. H. Niden, C. Mittman, R. C. Talley and W. R. Barclay. Non-uniform pulmonary diffusion as demonstrated by the carbon monoxide equilibration technique: experimental results in man. *J. clin. Invest.*, 1960, 39: 943-951.

2246. Carlsen, E. and J. H. Comroe, Jr. Rate of CO uptake by normal erythrocytes and by spherocytes. *Fed. Proc.*, 1955, 14: 25.

2247. Carlsen, E. and J. H. Comroe, Jr. The rate of uptake of carbon monoxide and of nitric oxide by normal human erythrocytes and experimentally produced spherocytes. *J. gen. Physiol.*, 1958, 42: 83-107.

2248. Forster, R. E., W. S. Fowler and D. V. Bates. Considerations on the uptakes of carbon monoxide by the lungs. *J. clin. Invest.*, 1954, 33: 1128-1134.

2249. Forster, R. E., W. S. Fowler, D. V. Bates and B. VanLingen. The absorption of carbon monoxide by the lungs during breathholding. *J. clin. Invest.*, 1954, 33: 1135-1145.

2250. Forster, R. E., F. J. W. Roughton, L. Cander, W. A. Briscoe and F. Kreuzer. Apparent pulmonary diffusing capacity for CO at varying alveolar O<sub>2</sub> tensions. *J. appl. Physiol.*, 1957, 11: 277-289.

2251. Forster, R. E., F. J. W. Roughton, F. Kreuzer and W. A. Briscoe. Photocolorimetric determination of rate of uptake of CO and O<sub>2</sub> by reduced human red cell suspensions at 37°C. *J. appl. Physiol.*, 1957, 11: 260-268.

2252. French, N. and A. L. Hall. The time course of carboxyhemoglobin formation in subjects exposed to carbon monoxide for periods of ten to sixteen hours, and its modification by intermittent breathing of 100% oxygen. U.S. Navy. School of Aviation Medicine, Pensacola, Fla. *Res. Rept. NM 001 059.32.01*, 6 July 1954, 7 pp.

2253. Hanson, J. S. and B. S. Tabakin. Steady state carbon monoxide diffusing capacity in normal females. *J. appl. Physiol.*, 1961, 16: 839-841.

2254. Joels, N. and L. G. C. E. Pugh. The carbon monoxide dissociation curve of human blood. *J. Physiol.*, 1958, 142: 63-77.

2255. Moore, N. M., T. C. Smith, P. I. Sunahara and I. Rankin. A new concept of the physiological factors influencing the absorption of CO by the human lung. *Fed. Proc.*, 1961, 20: 424.

2256. Rankin, I., R. S. McNeill and R. E. Forster. Influence of increased alveolar CO<sub>2</sub> tension on pulmonary diffusing capacity for CO in man. *J. appl. Physiol.*, 1960, 15: 543-549.

2257. Roughton, F. J. W. The equilibrium between carbon monoxide and sheep haemoglobin at very high percentage saturations. *J. Physiol.*, 1954, 126: 359-383.

2258. Shepard, R. H., H. B. Martin, H. A. White, S. Permutt, E. Varnauskas and R. L. Riley. Comparison of estimates of pulmonary diffusing capacity by steady-state methods using oxygen and carbon monoxide in normal subjects at different levels of exercise. *Fed. Proc.*, 1958, 17: 147.

2259. Smith, T. C. and I. Rankin. The effects of respiratory maneuvers on the uptake of carbon monoxide and calculated diffusing capacity during breathholding. *Fed. Proc.*, 1960, 19: 382.

2260. Turino, G. M., M. Brandfonbrener, R. M. Goldring and A. P. Fishman. Influence of inspired O<sub>2</sub> tension on pulmonary diffusing capacity for CO. *Fed. Proc.*, 1957, 16: 129.

2261. Turino, G. M., E. H. Bergofsky and A. P. Fishman. Maximum diffusing capacity of the lung for oxygen and carbon monoxide. *Fed. Proc.*, 1958, 17: 164.

2262. Wald, G. and D. W. Allen. The equilibrium between cytochrome oxidase and carbon monoxide. *J. gen. Physiol.*, 1957, 40: 593-608.

2263. Wilks, S. S. Reactions of normal, altitude-acclimatized and CO-acclimatized animals to local injections of pure carbon monoxide gas. *Fed. Proc.*, 1954, 13: 165.

## 6. TOLERANCE AND ACCLIMATIZATION TO CARBON MONOXIDE

It appears that some acclimatization to carbon monoxide may occur without evidence of a hematopoietic response. According to Clark and Otis (2264) 1952, mice that had been acclimatized to concentrations of carbon monoxide up to 0.15 percent for 14 days can survive an acute exposure to 34,000 feet altitude considerably longer than mice unacclimatized to carbon monoxide. Mice which have been exposed to low oxygen for 14 days can survive in an atmosphere containing 0.25 percent carbon monoxide considerably longer than mice unacclimatized to low oxygen. The oxygen capacity and hematocrit in the authors' experiments increased to about the same extent for the mice acclimatized to low carbon monoxide and to low oxygen. The oxygen capacity increased about 50 percent above the controls and the hematocrit 85 percent. The carbon dioxide capacity of the plasma was found to decrease for the mice acclimatized to low oxygen. Mice acclimatized to low carbon monoxide showed a higher carbon dioxide capacity than unacclimatized mice. In studies by Weeks (2265) 1962, dogs, rats and rabbits were exposed to 50.9 ppm carbon monoxide for three months with carbon dioxide content ranging between 600 and 1300 ppm and ammonia from 20 to 50 ppm. The carbon monoxide content of the blood was 6.4 percent saturation of hemoglobin for dogs, 3.0 percent for rabbits and 1.6 percent for rats. The dogs showed a rise in hemoglobin of 12 percent, in



hematocrit of 9 percent and a possible increase in red blood cells, perhaps indicating some acclimatization and giving the only indication of a possible metabolic response to 50 ppm carbon monoxide. There was a small increase in eosinophil count in rats. No significant differences between exposed and control animals were found in reticulocytes, WBC's, differentials, macroscopic and microscopic examinations of organs and tissues respectively, or in behavior or activity. After a 24 hour exposure of dogs to carbon monoxide the formation of carboxyhemoglobin was 6 percent saturation of hemoglobin with 50 ppm of carbon monoxide, 12.6 percent with 100 ppm, 21 percent with 200 ppm and 31 percent with 300 ppm.

2264. Clark, R. T., Jr. and A. B. Otis. Comparative studies on acclimatization of mice to carbon monoxide and to low oxygen. *Amer. J. Physiol.*, 1952, 169: 285-294.

2265. Weeks, M. H. Effects of chronic exposure to low concentrations of carbon monoxide. pp. 347-349 in: *Man's dependence on the earthly atmosphere*. Edited by K. E. Schaefer, The MacMillan Company, New York, 1962, 416 pp.

## 7. TREATMENT

This section will include a selection of reports on treatment of carbon monoxide poisoning by the use of carbogen, oxygen at ambient pressures, oxygen at pressures greater than one atmosphere and succinic acid. Douglas, Lawson, Ledingham, Norman, Sharp and Smith (2266) 1961, have carried out experimental studies on the use of carbogen in experimental carbon monoxide poisoning. Two groups of 10 dogs were gassed with carbon monoxide until the level of carboxyhemoglobin was 70 percent. Animals were then resuscitated using 5 and 7 percent carbogen in turn. When a non-return valve was placed in a resuscitation circuit no difference was found between the efficacy of 5 and 7 percent carbogen. Thus the choice of a respiratory valve which prevents rebreathing when resuscitation is undertaken in carbon monoxide poisoning is of more importance than the choice of 5 or 7 percent carbogen mixture. The same authors (2267) 1962, found that treatment of carbon monoxide poisoning in dogs with pure oxygen at two ATA was by far the most efficient. Next in order was 5 or 7 percent carbogen. Least effective was pure oxygen alone. Lawson, Mc-

Allister and Smith (2271) 1961, also treated animals with acute carbon monoxide poisoning by oxygen under pressure. Rats and cats were exposed to 3 percent carbon monoxide in air and showed ataxia after two minutes. The animals were unconscious after 3-4 minutes and died in 5-13 minutes. Animals rendered unconscious by 3 percent carbon monoxide could be revived with oxygen at a pressure of 15 psi. Simultaneous exposure to 3 percent carbon monoxide and oxygen at 15 psi prevented evidence of carbon monoxide poisoning. It was suggested that oxygen under pressure not only increased plasma carriage of oxygen in solution but also altered the equilibrium mixture of carboxy- and oxyhemoglobin in favor of the latter. Heparinized human and equine blood exposed to coal gas by bubbling for 20 minutes contains high levels of carboxyhemoglobin which is liberated slowly when filmed in air, faster in one atmosphere of oxygen and fastest in two atmospheres oxygen. Four anesthetized dogs inhaled carbon monoxide for one to two hours with considerable respiratory depression. Using artificial respiration, carbon monoxide was liberated most rapidly with oxygen at two atmospheres, distinctly slower with oxygen at normal atmospheric pressure or with carbogen, and least rapidly in air alone. Fresh air may be sufficient in mild cases of carbon monoxide poisoning, but in severe cases the twin aims of immediate adequate oxygenation of the tissues, and rapid elimination of the gas can be carried out most effectively using artificial respiration with oxygen at a pressure of two ATA. The treatment of patients with carbon monoxide poisoning with oxygen at two atmospheres pressure has been described by Smith, Ledingham, Sharp, Norman and Bates (2276) 1962. Thirty-two patients with coal gas poisoning were admitted to the Western Infirmary, Glasgow, during a 12 month period. All of these recovered completely. Twenty-two of these patients who appeared to be severely gassed were treated within 30 minutes after exposure in a pressure chamber where they breathed oxygen at two ATA through face masks. This form of treatment rapidly corrected the anoxia and increased the speed at which carbon monoxide was removed from the blood and tissues. High pressure therapy was believed

by the authors to be particularly beneficial in cases complicated by cerebral depression from barbiturate overdose or in states of diminished cerebral blood flow. Experimental use of succinic acid in the treatment of acute carbon monoxide poisoning has been described by Gershon, Trethewie and Crawford (2268) 1961. This substance was injected intraperitoneally into cats and guinea pigs comatose from exposure to coal gas, producing marked respiratory improvement and greatly increased rate of recovery. In dogs intravenous administration of succinic acid produced an immediate return to a normal level of consciousness and reversed electrocardiographic changes due to carbon monoxide poisoning.

2266. Douglas, T. A., D. D. Lawson, I. McA. Ledingham, J. N. Norman, G. R. Sharp and G. Smith. Carbogen in experimental carbon-monoxide poisoning. *Brit. med. J.*, 1961, 5268: 1673-1675.

2267. Douglas, T. A., D. D. Lawson, I. McA. Ledingham, J. N. Norman, G. R. Sharp and G. Smith. Carbon monoxide poisoning: a comparison between the efficiencies of oxygen at one atmosphere pressure, of oxygen at two atmospheres pressure, and of 5% and 7% carbon dioxide in oxygen. *Lancet*, 1962, 1: 68-69.

2268. Gersohn, S., E. R. Trethewie and M. Crawford. The use of succinic acid in the treatment of acute carbon monoxide poisoning. *Arch. int. Pharmacodyn.*, 1961, 134: 16-27.

2269. Jacobinzer, H. and H. W. Raybin. Carbon monoxide poisoning. *N.Y. St. J. Med.*, 1962, 62: 2714-2716.

2270. Lawson, D., R. A. McAllister and G. Smith. The effect of high pressure oxygen in experimental acute carbon monoxide poisoning. *Scot. med. J.*, 1959, 4: 327.

2271. Lawson, D. D., R. A. McAllister and G. Smith. Treatment of acute experimental carbon-monoxide poisoning with oxygen under pressure. *Lancet*, 1961, 1: 800-802.

2272. Löyning, Y. Oksygen-overtrykks-behandling ved kulloksydforgiftning. [Treatment with oxygen under pressure in carbon monoxide poisoning.] *Tidsskr. norske Laegeforen.*, 1961, 81: 1207-1208.

2273. Rapport, K. M. O lechenii otravlenii okis'iu ugleroda kislorodom pod povyshennym davleniem. [On the treatment of carbon monoxide poisoning with oxygen under increased pressure.] *Vo-med. Zh.*, 1958, 8: 46-49.

2274. Sluyter, M. E. The treatment of carbon monoxide poisoning by administration of oxygen at high atmospheric pressure. *Proc. R. Soc. Med.*, 1963, 56: 1002

2275. Sluyter, M. E. and I. Boerema. Treatment of carbon monoxide poisoning by administering pressurized oxygen. *Ned. Tijdschr. Geneesk.*, 1962, 106: 826-829.

2276. Smith, G., I. McA. Ledingham, G. R. Sharp, J. N. Norman and E. H. Bates. Treatment of coal-gas poisoning with oxygen at 2 atmospheres pressure. *Lancet*, 1962, 1: 816-819.

2277. Smith, G. and G. R. Sharp. Treatment of carbon-monoxide poisoning with oxygen under pressure. *Lancet*, 1960, 2: 905-906.

2278. Smith, G., G. R. Sharp and I. McA. Ledingham. Treatment of coal gas poisoning in humans by oxygen under pressure. *Scot. med. J.*, 1961, 6: 339.

2279. Tomashefski, J. F. and C. E. Billings, Jr. Carbon monoxide poisoning. The physiologic basis for treatment. *Ohio St. med. J.*, 1961, 57: 149-154.

## B. STIBINE

Antimony hydride ( $\text{SbH}_3$ ), known as anti-moniuretted hydrogen and later as stibine, was discovered by Thomson working in England and independently by Pfaff in Germany in 1837. Both of these investigators were studying the March test for arsenic.

Since battery grids often contain from 5 to 10 percent antimony, the production of stibine in perceptible quantities during overcharging of batteries is a potential hazard in submarines. Since the nuclear submarines are not as dependent on battery power as the older fleet-type boats, this hazard has been almost completely obviated by the new source for machinery power. A more comprehensive review of this subject was provided in Volume II of this Sourcebook.

2280. Doig, A. T. (Arseniuretted hydrogen poisoning in tank cleaners. *Lancet*, 1958, 2: 88-92.

2281. Gt. Brit. MRC. Hazard from stibine. Gt. Brit. MRC, RNPRC, SMS. *Rept. S.M.S.* 22, 2 pp.

2282. Sax, N. I., L. J. Goldwater, B. Feiner, M. B. Jacobs, J. H. Harley, J. J. Fitzgerald and M. S. Dunn. Antimony hydride. p. 454 in: *Dangerous properties of industrial materials*. Reinhold Publishing Corp., New York, 1343 pp.

## C. OZONE

Ozone, according to Von Oettingen (2306), is a faintly blue gas when pure and has an odor like hay, but when contaminated becomes acrid and irritating. The gas causes irritation to the respiratory tract, resulting in coughing, frontal headache and sometimes nausea. Continued exposure leads to fatigue, somnolence, disturbed sleep, loss of appetite, oppression of the chest, vomiting, and later pulmonary edema and even death may result. This gas may be present in modern submarines (2284), having been produced by electrostatic precipitators and other arcing electrical equipment on the boat. It therefore presents a hazard. Early reports demonstrated that exposure to 0.4 percent ozone killed



animals in one minute. Autopsy revealed severe pathological alterations in the lung. In general, concentrations of ozone greater than 0.1 ppm are toxic, and the lung seems to be the only organ affected. Carbon dioxide excretion and oxygen uptake by the lung are reduced. Transfusions of blood from an ozonized animal did not produce symptoms in the transfused animal. Subtoxic concentrations of the gas produce irritation of the eyes and respiratory tract. Exposure to 6 ppm for one hour reduced the vital capacity to 57.7 percent of normal (5035 and 2905 cc.) and the residual capacity was increased by 840 cc. This was explained by partial filling of alveolar sacs with edematous fluid while swelling of the bronchioles was thought to prevent complete opening of the bronchioles into the alveoli. Thorp (2305) 1950, has pointed out that the toxicity of ozone is greatly enhanced by contamination with nitrogen oxides. An excellent review of the literature on ozone toxicity through 1953 has been published by Stokinger (2301) 1954. Patty (2298) 1958, has listed the following thresholds for ozone: Threshold for odor 0.01–0.015 ppm; maximum allowable concentration 0.04 ppm; disorders of breathing and reduced oxygen consumption 0.5–1.0 ppm; inhibition of fungal growth 0.3–1.5 ppm; headache, respiratory irritation 1–10 ppm; lethal to small animals within 2 hours 15–20 ppm; germicidal for airborne organisms 6500 ppm.

According to Mittler, King and Burkhardt (2296) 1957, repeated exposure to 2.4 ppm of ozone induced some hemorrhage and edema in the lungs of rats. Adaptation to ozone is noticed after 32 hours of accumulative exposure. Twenty percent of 102 mice died after continued exposure to 2.4 ppm of ozone for 241 hours. Chronic exposure to ozone decreased weight gain by young rats and concentrations greater than 1.2 ppm and longer than 7 hours per day significantly affected growth of young rats. The 0.1 ppm value as a maximum allowable concentration of ozone for an 8 hour workday appears reasonable. Mittler, Hedrick, King and Gaynor (2294) 1956, have also demonstrated species differences in ozone toxicity. The  $LD_{50}$  for a three hour exposure of ozone was found to be 21 ppm for mice, 21.8 ppm for rats, 34.5 ppm for

cats, 36 ppm for rabbits and 51.7 ppm for guinea pigs. Edema occurred in lungs of rats exposed to 6 ppm for eighteen hours. No damage was caused by 24 hour exposure to concentrations of less than 3 ppm of ozone.

Clamann and Bancroft (2285) 1957, have called attention to the confusion in the literature on the actual toxicity of ozone. With respect to the ever increasing importance of ozone for industrial purposes and the presence of ozone in the upper atmosphere as a possible hazard in high altitude conditions, accurate data on the physiological effects of ozone are very desirable. In animals it was found that for a three hour exposure time the  $LD_{50}$  was 12.6 ppm by volume for mice, and 25.7 ppm for guinea pigs. Death was caused by edema and hemorrhage of the lungs. Studies on five human subjects revealed great differences in human sensitivity. Irritation of the respiratory tract was observed at concentrations as low as 0.6 ppm after 30 minutes. Gross changes of respiratory function (reduction of vital capacity in more than 50 percent and pulmonary edema) occurred after one hour at 6 ppm. The soft tissues of the respiratory tract seem to be the only tissues of the body attacked by ozone. The sense of smell is definitely affected. An effect on the conjunctiva of the eye was neither felt nor observed by inspection. No effects upon blood and the circulatory system were found. Stokinger, Wagner and Dobrogorski (2302) 1957, also found chronic injury as a result of repeated inhalation of ozone at concentrations only 2–3 times greater than currently reported in urban areas. The injury is characterized pathologically as chronic bronchitis and bronchiolitis. In this condition the terminal airways of the lungs were thickened, the air passages narrowed, with fibrotic tissue extending into the surrounding areas of the lungs with consequent emphysema resulting in a lessened capacity to move air in and out of the lungs. The dog showed none of these deep lung changes seen in the smaller animals. Man's relative position in this range of pulmonary response to ozone was judged to be between that of the dog and the smaller animals. Griswold, Chambers and Motley (2291) 1957, reported the case of one author who spent two hours in a chamber exposed to 2 ppm ozone. Twenty-two hours later

on the following day there was a 13 percent reduction in the total vital capacity with return to normal after 22 hours. In studies reported by Young and Shaw (2307) 1963, eight normal men in twelve experiments breathed air from a breathing circuit while seated for two hours and then breathed air containing 0.6-0.8 ppm of ozone for two hours from the same circuit. There was a slight reduction of vital capacity from which the authors concluded that breathing less than 1 ppm of ozone for two hours does produce a significant but reversible reduction of steady state  $D_{\text{LCO}}$  in normal subjects.

Kleinfeld and Giel (2292) 1956, reported three cases of ozone poisoning in welders employing a new welding technique. There is difficulty in diagnosis in view of a number of clinical conditions resembling ozone poisoning, such as acute pulmonary edema, pulmonary infarction, acute myocardial infarction, bronchial asthma, and bronchial pneumonia, as well as pulmonary inflammatory conditions due to other toxins such as phosgene. The diagnosis of ozone poisoning may be suspicious and depend on adequate occupational history, familiarity with the toxicological effects and finding significant amounts of ozone in the working environment. In the cases reported, the presence of 9.2 ppm of ozone at the work site was far in excess of the presently accepted threshold limit of 0.1 ppm. Regarding the effect of oxygen and carbon dioxide upon the acute toxicity of ozone, Mittler, Hedrick and Phillips (2295) 1957, found that ozone in oxygen was less toxic for mice than ozone in air. The oxygen had no influence on toxicity of ozone for rats and guinea pigs. Ozone in 2 percent carbon dioxide-air mixture was more toxic for guinea pigs than ozone in air. The two percent carbon dioxide had no significant effect on the toxicity of ozone for rats and mice.

In further studies of ozone toxicity Stokinger, Wagner and Wright (2303) 1956, found a striking enhancement of toxicity of ozone in rats and mice when the animals were exercised intermittently during exposure. Thus an ozone concentration of 1 ppm was fatal in six hours in these species when accompanied by exercise for 15 minutes each hour of exposure. The authors found that marked tolerance to ozone developed rapidly (within 24 hours) and persisted for 4-6 weeks.

Treatment is symptomatic and the condition is best dealt with by prevention. Fairchild, Murphy and Stokinger (2288) 1959, described two distinct but related pathways of protection against the lethal effects of ozone and nitrogen dioxide: a) simultaneous inhalation of compounds that furnish -SH or -SS groups or both, and b) by injection of thiourea derivatives several days prior to exposure to these oxidant gases. The mechanism of a) is believed similar to that proposed for the action of radiation protective compounds. That of b) involves the development of a tolerance initiated by the thiourea against the oxidants. A paper by Mittler (2297) 1958, also brings out the difficulty of therapy. In submarine operations the strategy must be to prevent the buildup of toxic levels of ozone in the atmosphere.

2283. Christensen, E. and A. C. Giese. Changes in absorption spectra of nucleic acids and their derivatives following exposure to ozone and ultraviolet radiations. *Arch. Biochem. Biophys.*, 1954, 51: 208-216.

2284. Clamann, H. G. Physical and medical aspects of ozone. pp. 143-156 in: *Physics and medicine of the atmosphere and space*. Edited by O. O. Benson, Jr. and H. Strughold, John Wiley and Sons, Inc., New York, 1960, 645 pp.

2285. Clamann, H. G. and R. W. Bancroft. Physiological effects of ozone. *Fed. Proc.*, 1957, 16: 22.

2286. Davis, I. Microbiologic studies with ozone. Quantitative lethality of ozone for *Escherichia coli*. USAF. Brooks Air Force Base, Texas. School of Aerospace Medicine, Rept. no. 61-54, March 1961, 16 pp.

2287. Diggle, W. M. and J. C. Gage. The toxicity of ozone in the presence of oxides of nitrogen. *Brit. J. industr. Med.*, 1955, 12: 60-70.

2288. Fairchild, E. J., II, S. D. Murphy and H. E. Stokinger. Protection by sulfur compounds against the air pollutants ozone and nitrogen dioxide. *Science*, 1959, 130: 861-862.

2289. Forchheimer, O. L. and H. Taube. Tracer studies on the decomposition of ozone in water. *J. Amer. Chem. Soc.*, 1954, 76: 2099-2103.

2290. Giese, A. C., H. L. Leighton and R. Bailey. Changes in the absorption spectra of proteins and representative amino acids introduced by ultraviolet radiations and ozone. *Arch. Biochem. Biophys.*, 1952, 40: 71-84.

2291. Griswold, S. S., L. A. Chambers and H. L. Motley. Report of a case of exposure to high ozone concentrations for two hours. *Arch. industr. Hlth.*, 1957, 15: 108-110.

2292. Kleinfeld, M. and C. P. Giel. Clinical manifestations of ozone poisoning: report of a new source of exposure. *Amer. J. med. Sci.*, 1956, 231: 638-643.

2293. Mendenhall, R. M. and H. E. Stokinger. Surface active films as a model of lung injury by irritant gases. *Fed. Proc.*, 1961, 20: 420.



2294. Mittler, S., D. Hedrick, M. King and A. Gaynor. Toxicity of ozone. I. Acute toxicity. *Industr. Med.*, 1956, 25: 301-306.

2295. Mittler, S., D. Hedrick and L. Phillips. Toxicity of ozone. II. Effect of oxygen and carbon dioxide upon acute toxicity. *Industr. Med.*, 1957, 26: 63-66.

2296. Mittler, S., M. King and B. Burkhardt. Toxicity of ozone. III. Chronic toxicity. *Arch. industr. Hlth.*, 1957, 15: 191-197.

2297. Mittler, S. Toxicity of ozone. IV. Silicone aerosols and alcohol vapor therapy in ozone poisoning. *Industr. Med. Surg.*, 1958, 27: 43-45.

2298. Patty, F. A. Ozone. pp. 915-917 in: *Industrial hygiene and toxicology*. Volume II. Edited by F. A. Patty, Interscience Publishers, Inc., New York, 1958, 2377 pp.

2299. Sax, N. I. Ozone. p. 1064 in: *Dangerous properties of industrial materials*. Edited by N. I. Sax, Reinhold Publishing Corp., New York, 1963, 1343 pp.

2300. Spector, W. S. Ozone. p. 346 in: *Handbook of toxicology*. Volume I. U.S. National Research Council, W. B. Saunders Co., Philadelphia, 1956, 408 pp.

2301. Stokinger, H. E. Ozone toxicity. A review of the literature through 1953. *Arch. industr. Hyg.*, 1954, 9: 366-383.

2302. Stokinger, H. E., W. D. Wagner and O. J. Dobrogorski. Ozone toxicity studies. III. Chronic injury to lungs of animals following exposure at a low level. *Arch. industr. Hlth.*, 1957, 16: 514-522.

2303. Stokinger, H. E., W. D. Wagner and P. G. Wright. Studies of ozone toxicity. I. Potentiating effects of exercise and tolerance development. *Arch. ind. Hlth.*, 1956, 14: 158-162.

2304. Tamas, A. A. Threshold limit values for hydrocarbons and ozones in confined spaces. pp. 343-346 in: *Man's dependence on the earthly atmosphere*. Edited by K. E. Schaefer, The MacMillan Company, New York, 1962, 416 pp.

2305. Thorp, C. E. The toxicity of ozone. *Industr. Med.*, 1950, 19: 49-57.

2306. Von Oettingen, W. F. Ozone. pp. 470-471 in: *Poisoning. A guide to clinical diagnosis and treatment*. W. B. Saunders Co., Philadelphia, 1958, 627 pp.

2307. Young, W. A. and D. B. Shaw. Effect of low concentrations of ozone on pulmonary function. *Fed. Proc.*, 1963, 22: 396.

#### D. RADON

The following papers on radon have been included because of the potential hazard in closed spaces. However, at present in submarines radon is no longer used in luminous paint for dials.

2308. Martin, E. J. and J. K. W. Ferguson. Radon in normal breath. *Canad. J. med. Sci.*, 1952, 30: 42-47.

2309. Martin, E. J. and J. K. W. Ferguson. Fluctuations of breath. radon in subjects seated at rest. *Arch. industr. Hyg.*, 1953, 8: 574-581.

2310. Nussbaum, E. and J. B. Hursh. Radon solubility in fatty acids and triglycerides. *J. phys. Chem.*, 1958, 62: 81-84.

#### E. TOBACCO SMOKE

Since smoking is still a virtually universal habit and since the use of tobacco does have definite morale values, it is not desirable to restrict smoking except under certain conditions. Smoking does add to the carbon monoxide content of the air and this should be a limiting factor. The papers that follow are selected from the large literature on physiological effects of tobacco smoking. McGiff (2319) 1963, found in anesthetized dogs a three to thirty-fold increase in renal vascular resistance associated with a marked pressor response (range 75 to 150 mm./Hg increment). Femoral vascular resistance was only moderately increased. The response of the renal bed was examined in detail by measuring flows from both kidneys, one of which was denervated. Denervation did not preclude the increased renal vascular resistance. Adrenergic blocking agents (e.g. 0.1 mgm./kg. phentolamine) will prevent the pressor response or terminate an established pressor response concomitantly with restoration of renal flows to control levels. Ganglionic blocking agents, reserpine and adrenalectomy will prevent both the hypertensive response and the increase in renal vascular resistance. Shepherd (2324) 1951, found in human subjects that inhalation of tobacco smoke at intervals of one minute led to a transient decrease in hand blood flow at the time of inhalation. Similar decreases occurred when inhalations of the same depth were carried out with the cigarette unlit. Transient decrease in flow was therefore due to the physiological effect of the deep breath and was not necessarily caused by the pharmacological action of the substance in the tobacco. Apart from this decrease in flow on inhalation, the general level of hand flow was unaltered during and immediately after smoking one cigarette. When cigarette smoke was inhaled every 20 seconds, more rapidly than normal, the hand blood flow steadily decreased during the smoking period. When cigarettes were smoked at rates in excess of normal there was a resulting decrease in hand blood flow that was mainly pharmacological and not physiological in origin. In studies carried out by Wechsler (2325) 1958, normal subjects (17 to 85 years of age) smoked three regular sized cigarettes in 10 minutes. No significant

changes in cerebral blood flow, oxygen consumption, vascular resistance, respiratory quotient or blood pH were observed. Electroencephalograms were made before, during and for 10 minutes after smoking and revealed intermittent flattening, lasting for 1-30 seconds. This pattern only occurred with puffing on the cigarette. It also occurred to a lesser degree in individuals who did not inhale and in those subjects smoking filtered or denicotinized cigarettes. This pattern could be an abnormal attention response. Lung volumes in smokers and non-smokers have been reported by Blackburn, Brozed, Carlson and Taylor (2311) 1958. The subjects were 222 clinically healthy business and professional men aged 47-57 years. The mean age and relative body weight were similar in different categories of cigarette smokers and of non-smokers. Vital capacity and residual volume were measured with the subjects seated. In comparison with the non-smokers, all smokers showed smaller vital capacity, larger residual volume, smaller total lung capacity and larger ratio of residual volume to total lung capacity. The relation of lung volume to smoking is in the direction to be expected if smoking is a repeated source of bronchial irritation causing increased airway resistance. In 31 subjects who had successfully stopped all smoking one or more years prior to the experiment, the mean values were not significantly different from the category of subjects who had never smoked. In studies by Nadel and Comroe (2320) 1961, a body plethysmograph was used to measure the ratio of airway conductance (reciprocal of airway resistance) to thoracic gas volume in a group of healthy subjects, including 23 non-smokers and 25 smokers. The ratio decreased after inhalation of cigarette smoke in both groups and the effect was almost immediate, lasting about 35 minutes. Krumholz, Chevalier and Ross (2315) 1963, carried out an investigation designed to study the effect of chronic cigarette smoking on some aspects of pulmonary physiology and on the ability of the individual to handle and repay his oxygen debt during and after exercise. Studies were carried out in nine smokers and in nine non-smokers who were similar in body surface area, age and occupation. All smokers had smoked at least one pack a day for five years. Every subject

exercised for five minutes on a bicycle ergometer and a mean oxygen uptake of 2.06 L./minute was achieved during the fifth minute of work. The ratio of the oxygen debt to the total oxygen uptake was significantly greater in the smoking group than in the non-smokers. Resting breath-holding and pulmonary diffusing capacity was significantly greater in non-smokers than in smokers. In a study by Orma, Karvonen, Keys and Brozek (2321) 1958, in a group of male subjects aged 20-59 years of age and judged "healthy" from clinical and electrocardiographic examination, the serum cholesterol was significantly higher while the blood pressure tended to be lower in smokers as compared to non-smokers. Westfall and Watts (2326) 1963, found a significantly higher 24 hour urinary excretion of epinephrine in smokers than in non-smokers. The difference in nor-epinephrine excretion was not significant. In other studies the excretion of epinephrine and nor-epinephrine was determined at 30 minute intervals before, during and after heavy smoking in 15 subjects. The results indicated that the epinephrine and total catecholamine output increases progressively above control levels during periods of heavy smoking. Experiments were also carried out in which blood samples were obtained from the inferior vena cava above and below the adrenal glands in patients undergoing cardiac catheterization before, during and after smoking one cigarette. The results showed an increase in the epinephrine levels from the inferior vena cava blood from a control value of 1.2  $\mu\text{gm./L.}$  to a value of 3.7  $\mu\text{gm./L.}$  during smoking.

2311. Blackburn, H., J. Brozek, W. Carlson and H. L. Taylor. Lung volumes in smokers and non-smokers. *Fed. Proc.*, 1958, 17: 15.

2312. Brozek, J. and A. Keys. Smoking and body composition. *Fed. Proc.*, 1957, 16: 16.

2313. Haagen-Smit, A. J., M. F. Brunelle and J. Hara. Nitrogen oxide content of smoke from different types of tobacco. *Arch. industr. Hlth.*, 1959, 20: 399-400.

2314. Kratochvil, C. H., S. S. Wilks and W. A. Gerrard, III. Cigarette smoking at altitude. *Fed. Proc.*, 1957, 16: 75.

2315. Krumholz, R. A., R. B. Chevalier and J. C. Ross. Pulmonary diffusing capacity and oxygen debt at rest and during exercise in smokers and non-smokers. *Circulation*, 1963, 28: 754.



2316. Levine, R. R., E. W. Pelikan and C. J. Kensler. The effect of cigarette smoking on the excretion of phenol red. *Fed. Proc.*, 1961, 20: 414.

2317. Lyons, M. J. and H. Johnston. Chemical investigation of the neutral fraction of cigarette smoke tar. *Brit. J. Cancer*, 1957, 11: 544-562.

2318. Maliszewski, T. F. and D. E. Bass. 'True' and 'apparent' thiocyanate in body fluids of smokers and nonsmokers. *J. appl. Physiol.*, 1955-56, 8: 289-291.

2319. McGiff, J. C. Regional flow response to cigarette smoking in the dog. *Fed. Proc.*, 1963, 22: 509.

2320. Nadel, J. A. and J. H. Comroe, Jr. Acute effects of inhalation of cigarette smoke on airway conductance. *J. appl. Physiol.*, 1961, 16: 713-716.

2321. Orma, E., M. Karvonen, A. Keys and J. Brozek. Cigarette smoking, serum cholesterol and blood pressure. *Fed. Proc.*, 1958, 17: 120.

2322. Osborne, J. S., S. Adamek and M. E. Hobbs. Some components of gas phase of cigarette smoke. *Analyt. Chem.*, 1956, 28: 211-215.

2323. Rinfret, A. P. Effect of ionized air and tobacco smoke on the adrenal lipid content in rats. *Stanf. med. Bull.*, 1953, 11: 125.

2324. Shepherd, J. T. Effect of cigarette-smoking on blood flow through the hand. *Brit. med. J.*, 1951, 2: 1007-1010.

2325. Wechsler, R. L. Effects of cigarette smoking and intravenous nicotine on the human brain. *Fed. Proc.*, 1958, 17: 169.

2326. Westfall, T. C. and D. T. Watts. Catecholamine excretion in smokers and nonsmokers. *Fed. Proc.*, 1963, 22: 509.

### F. AIR IONS

It has been suggested that an excess of positive air ions may be partly responsible for reduced well being and efficiency. A large literature has developed in which this possibility is discussed. In a study of the effect of gaseous ions on tracheal ciliary rate, Krueger and Smith (2347) 1958, have pointed out that positive and negative air ions have notable effects upon ciliary rate and other properties of the mammalian trachea both *in vitro* and *in vivo*. It seems reasonable, according to the authors, to conclude that these effects stem from physiologically significant alterations in the state of gases present in the ambient atmosphere and that deliberately produced changes in composition of the atmosphere will be reflected in the response of the tracheal tissue. To test this assumption experiments were performed on rabbits. The experiments demonstrated that when administered in unmodified humid air, negative ions increase the ciliary rate by about 200 beats per minute reaching maximum effect

within 10-20 minutes, while positive air ions lower the ciliary rate by about 300 beats per minute or abolish ciliary activity altogether (reaching maximum effect within 15-20 minutes). These effects were seen both in tracheas of living animals and in extirpated tracheal strips. In similar studies Krueger and Smith (2345) 1957, carried out experiments to determine whether negative ions were beneficial in certain cases of hay fever and asthma, while positive ions produce nasal obstruction, dryness of mucous membranes and headaches. The experiments were also designed to test whether these observations could be correlated with measurable changes in pulmonary clearing mechanisms including ciliary rate, rate of mucous flow and smooth muscle tone. Ciliary activity became slowed and ceased usually in six hours with exposure of tracheal strips to positive ions. Negative ions produced increased ciliary rate. Exposure to positive ions caused the mucous flow to decrease markedly or to cease. Negative ions caused an increase in one-half of the experiments and no effect in the other half. Positive ions routinely caused the membranous posterior wall of the trachea to contract. In this condition it was possible to elicit peristalsis by stretching the tissue laterally. Negative ions completely reversed this effect. On exposure to positive ions the tracheal surface assumed a dry, non-glossy appearance, whereas negative ions either had no effect or caused the appearance of watery fluid. Positive ions rendered the cilia particularly vulnerable to mechanical trauma. This completely disappeared when the tissue was exposed to negative ions. All of these studies were carried out on rabbit tissue, and the authors point out that no theory has yet been developed for the action of air ions on the trachea. Krueger and Smith (2351) 1962, have concluded that air ions are unquestionably physiological mediators, positive ions being harmful and negative ions beneficial. Ion-induced changes in the physiological state of the trachea tend to persist. After 72 hours in a positively ionized environment, mice retained the effects for four weeks. Tracheal effects attributed to positive ions can be duplicated by intravenous injection of 5-hydroxytryptamine and like positive ions, effects can be reversed by treatment with negative air ions.

Therefore, positive air ions appear to be "serotonin releasers" and a local accumulation of 5-hydroxytryptamine is the immediate cause of positive ion effects. That negative ion reversal of positive ion effects is by increasing the rate of 5-hydroxytryptamine oxidation is supported by the direct action of negative ions on cytochrome oxidase and acceleration of the cytochrome-linked conversion of succinate to fumarate. Reserpine which causes tissue depletion of 5-hydroxytryptamine, has an effect on the trachea similar to negative ions and positive ions have no effect on reserpine-treated animals. Iproniazid blocks the enzyme responsible for metabolizing 5-hydroxytryptamine and an accumulation of 5-hydroxytryptamine develops. An iproniazid treated animal displays tracheal effects resembling those produced by positive air ions and resists the normal action of negative air ions in reversing this effect. A similar report has been given by Krueger and Smith (2350) 1960. Nielsen and Harper (2361) 1954, have studied the effect of air ions on succinoxidase activity of rat adrenal glands. After four hours in positively ionized air the succinoxidase content of the rat's adrenal gland was significantly reduced. A similar period in negatively ionized air produced slight but insignificant rise in succinoxidase activity. By comparison, a single injection of 5 mgm. of ACTH produced a moderate rise whereas the same dose given twice daily for six days resulted in a significant fall in adrenal succinoxidase. According to Worden (2374) 1954, exposure of young adult male hamsters to positive air ion concentrations decreased the carbon dioxide capacity of the blood whereas exposure to negative air ions increased the carbon dioxide capacity of blood. In both cases the changes were significantly different from controls. Worden and Thompson (2375) 1956, found that the rate of proliferation of cultures of pure strain L cells (Earle's) was accelerated under conditions of negative ionization and decelerated under conditions of positive ionization. The nature of these effects is compatible with those observed in intact animals. Worden (2373) 1953, studied the effect of unipolar ionized air on the growth of selected organs of the Gold hamster. Ninety-two of these animals divided into three groups lived in ion controlled or a normal atmosphere

for 60 or more days of the postnatal development period. It was found that an atmosphere with an increased concentration of negative ions exerted a stimulating influence on the growth and ultimate relative weights of certain organs as compared with the same organs in control animals. An increased concentration of positive ions demonstrated no statistically significant values. Jordan and Sokoloff (2339) 1959, examined the effect of air ionization on maze learning in rats. A multiple T-pattern maze with escape from water was used on 150 rats of an average of three months of age and 150 rats of an average of 22 months of age in a study of age differences in maze learning. It was found that the number of errors and the time scores of the group of old rats were about three times and two times greater respectively than those of the young rat group under normal atmospheric conditions. Negative air ionization reduced considerably the number of errors and the time scores of the runs of the old rats. The psychological effects of artificially produced air ions in human subjects have been examined by McGurk (2355) 1959. Ten college age males were subjected to five hours exposure at specific work tasks under two environments: 1) approximately 8000 negative air ions/cc. of air, and 2) natural ion concentration of the test room. Some subjects also performed two hours of the same work in environments of approximately 8000 positive ions/cc. of air. There was no statistically significant difference in the mean scores of performance in the various conditions. The subjects were not able to respond accurately to the question, "Was the air ionized today?" when control conditions prevailed judgments differed from chance at the 1 percent level; when positive conditions prevailed judgments differed at the 10 percent level. Although the findings are tentative there was general agreement with previous literature that negative ionization environments were associated with feelings of well being and that positive ionization was associated with irritation, depression and fatigue.

The use of negatively ionized air in the treatment of burns has been reported by David, Minehart and Kornblueh (2330) 1960, and by Minehart, David and Kornblueh (2356) 1958. It appears that in a large number of the cases there



is relief of pain, reduction of local infection, decrease in exudation and deodorization of the burned area. Accelerated epithelialization has also been observed. Kornblueh, Piersol and Speicher (2343) 1958, reported relief from hay fever symptoms in 123 patients exposed to negative ionization. Positive ionization provided either no relief or increased distress. The relief obtained from negative ionization is said to be temporary since the symptoms reappear shortly after the individual returns to an environment with the normal ion balance.

2327. Behounek, F. and J. Kletschka. Ionization of air in an air-conditioned building. *Nature, Lond.*, 1938, 142: 956.

2328. Chase, C. T. and C. H. Willey. A biological effect of ionized air. *Science*, 1935, 82: 157-158.

2329. Cupcea, S., M. Deleanu and T. Frits. Experimentelle Untersuchungen über den Einfluss der Luftionisation auf pathologische Veränderungen der Magenschleimhaut. *Acta biol. med., Germ.*, 1959, 3: 407-416.

2330. David, T. A., J. R. Minehart and I. H. Kornblueh. Polarized air as an adjunct in the treatment of burns. *Amer. J. phys. Med.*, 1960, 39: 111-113.

2331. Deleanu, M. and T. Frits. Versuche über die Beteiligung des Nervensystems im biologischen Wirkungsmechanismus von ionisierter Luft. *Acta biol. med., Germ.*, 1961, 6: 103-109.

2332. Dougherty, J. H., K. E. Schaefer and W. Anderson. Interaction of airions and aerosols. *Fed. Proc.*, 1961, 20: 210.

2333. Duffner, G. J. Man-made air. Problems and limitations. *Ann. Otol., etc., St. Louis*, 1961, 70: 410-417.

2334. Edstrom, G. Studies in natural and artificial atmospheric electric ions. *Acta med. scand.*, 1935, 61: 1-83.

2335. Frey, A. H. Human behavior and atmospheric ions. *Psychol. Rev.*, 1961, 68: 225-228.

2336. Golovanova, G. P. and G. S. Gracheva. K voprosu o vliianii gidroaeroionizatsii na sostoianie zdorov'ia i razvitie detei rannego vozrasta. [On the effect of hydroaeroionization on the health status and growth of young children.] *Pediatrics, Moscow*, 1961, 1: 24-28.

2337. Herrington, L. P. The influence of ionized air upon normal subjects. *J. clin. Invest.*, 1935, 14: 70-80.

2338. Hinchcliffe, R. Some aspects of nasal function and dysfunction in relation to environmental air. *Ann. occup. Hyg.*, 1961, 3: 6-21.

2339. Jordan, J. and B. Sokoloff. Air ionization, age, and maze learning of rats. *J. Geront.*, 1959, 14: 344-348.

2340. Karmen, A., L. Giuffrida and R. L. Bowman. Detection by ionization of atmospheric gases during analysis by gas chromatography. *Nature, Lond.*, 1961, 191: 906-907.

2341. Koiranskii, B. B., L. Ia. Ukvol'berge, M. V. Dmitriev and N. S. Kolodina. O vliianii ionizatsii vozdukh na fizicheskuiu rabotosposobnost'. [On the effect of ionization of air on physical efficiency.] *Gigiena San., Moskva*, 1961, 7: 29-33.

2342. Kornblueh, I. H. and J. E. Griffin. Artificial air ionization in physical medicine: preliminary report. *Amer. J. phys. Med.*, 1955, 34: 618-631.

2343. Kornblueh, I. H., G. M. Piersol and F. P. Speicher. Relief from pollinosis in negatively ionized rooms. *Amer. J. phys. Med.*, 1958, 37: 18-27.

2344. Krueger, A. P. Some biologic properties of gaseous ions. *J. Einstein med. Cent.*, 1960, 8: 79-88.

2345. Krueger, A. P. and R. F. Smith. Effects of air ions on isolated rabbit trachea. *Proc. Soc. exp. Biol., N.Y.*, 1957, 96: 807-809.

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## VIII. MOTION SICKNESS

The subject of motion sickness was covered quite fully in Volume II of this Sourcebook. Since that time, however, the emergence of the nuclear powered boat has made it practical to travel submerged for prolonged distances, and this has obviated the necessity of running on the surface where stormy conditions may prevail. Therefore at present, and increasingly in the future, motion sickness problems in submarining may be considered to be abated. The following items have been included primarily for their academic interest. The factors which determine vulnerability to motion sickness seem to be neurophysiological rather than psychological, although psychological factors may play a role.

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## IX. SUBMARINE ESCAPE PROCEDURES

### A. BREATH HOLDING

Breath control is of importance in the correct practice of free escape under emergency conditions or in training. Breath control is also important to the SCUBA diver in certain emergencies such as exhaustion of the breathing gas tanks or malfunction of the breathing apparatus. Free escape is now the standard practice for individualized emergence from disabled submarines, and since buoyancy is now provided by an inflatable life vest, problems of buoyancy and ascent are obviated. Correct breath control is absolutely essential, the procedure being expressed colloquially as "blow and go". This means that the submariner exhales continuously throughout the ascent.



Breath holding is an important skill to escape tank instructors who must make free dives from the surface of the tank to observe the trainees as they perform their maneuvers. For this purpose they may have to hold a breath for three or four minutes. Skill in breath holding can be acquired and the duration of breath holding can be increased by practice.

Breath holding is part of the occupational skill of pearl and sponge divers and in some parts of the world, as in Japan and Korea, this work is undertaken by women who maintain a long tradition for this kind of activity.

For a sound review paper on breath holding, DuBois (2396) 1955, may be consulted. As pointed out in this review, breath holding is impossible with a  $P_{CO_2}$  greater than 60 mm. Hg, even with a normal  $P_{O_2}$  and lung volume. Breath holding is also impossible with  $P_{O_2}$  less than 30 mm. Hg (with other factors normal). A  $P_{CO_2}$  of 76 mm. Hg at full inspiratory tidal volume or 37 mm. Hg at full expiratory volume will terminate slow voluntary rebreathing. Just under the surface of the water, breath holding is impossible after the carbon dioxide has risen to 50 mm. Hg and the oxygen has fallen to 50 mm. Hg (about 50 seconds). At 100 feet (4 ATA) 60 mm. Hg carbon dioxide can be tolerated because of adequate oxygen saturation. Breath holding during depth changes are calculated on the basis of the rate of gas entering the pulmonary blood. This is equal to the A-V content difference times blood flow and is also dependent on the relationship of the rate of change, which equals the rate of change of concentration times volume. On ascent from 100 feet ( $1\frac{1}{4}$  minutes), starting with normal alveolar air and lung volume (4.7 liters), there is a decrease in  $P_{CO_2}$  which is due to expansion and to oxygen consumption. There is no rise in the alveolar  $P_{CO_2}$  because expansion just counteracts the metabolic rise as carbon dioxide is brought to the lungs by the venous blood. During rapid ascent after three minutes breath holding at 100 feet there is some danger of the  $P_{CO_2}$  falling to a low level during the last few feet. A subject short of breath at 100 feet is actually relieved by ascent. The rate of ascent should increase as the rate of carbon dioxide production is increased by actively swimming. During descent to 100 feet at one foot per second, the  $P_{CO_2}$

reaches 61 mm. Hg at 20 feet, and at two feet per second reaches 69 mm. Hg at 30 feet. The alveolar oxygen is always high, but these levels of carbon dioxide are dangerous. As the depth increases, the rate of compression is less, and the effect of blood flow in taking excess carbon dioxide out of the lungs is greater because of the small lung volume. A given amount of carbon dioxide taken out of a small lung volume decreases the  $P_{CO_2}$  to a greater degree.

Rahn has cited some unpublished data on Korean Amas diving to 30 feet in the Yellow Sea. These data were derived from his own investigations. Gas samples indicated that about 20 seconds after the beginning of the Ama's breath hold dive the total amount of carbon dioxide in her lungs was less than she had at the start of her dive, and the alveolar  $P_{O_2}$  was nearly as high as the inspired air at the surface. Of particular interest was the alveolar oxygen concentration on reaching the surface at the end of a 45–60 second dive. Values as low as 3.5 percent were recorded. The rapid expansion of the gases during the ascent caused the alveolar  $P_{O_2}$  to fall below the mixed venous level and therefore the usual direction of oxygen transport was reversed. During compression the  $P_{CO_2}$  in arterial blood increases above the values of mixed venous  $P_{CO_2}$  and remains elevated. The usual drop in  $P_{O_2}$  is prevented by compression. Therefore at this time the  $P_{CO_2}$  is the only important stimulus to respiration. Subjectively this is the hardest time of voluntary apnea. Upon ascent the arterial  $P_{CO_2}$  drops and brings immediate relief, but the  $P_{O_2}$  falls to very low levels and may drop so rapidly that the impairment of consciousness does not allow the full effect of the low oxygen drive to be experienced. The mental confusion just before reaching the surface makes such subjective analysis difficult.

Craig (2387) 1961, has given case reports of eight survivors and of five deaths from loss of consciousness. All of the victims were considered good swimmers and were experienced in underwater swimming. All of the survivors hyperventilated before going under the surface. Seven of these had some goal in mind or were in competition with others. Swimmers usually experienced an urge to breathe but there was little or no warning before "passing out". Cerebral

function was such that the victims were unable to take appropriate action to meet the situation. The author conducted experiments to attempt to explain why a person might lose consciousness while swimming under water. Prior hyperventilation increases breath holding time. During voluntary overbreathing  $P_{CO_2}$  in the blood is decreased as well as other carbon dioxide stores. During breath holding, plus exercise, metabolically produced carbon dioxide raises the  $P_{CO_2}$  in the blood. The rate of repletion of stores will limit the time at which blood  $P_{CO_2}$  attains levels associated with the overwhelming urge to breathe again. In humans the contribution of oxygen to the respiratory drive is weak. When the oxygen consumption is increased, as in the first few seconds of exercise, the  $P_{O_2}$  may decrease to a degree incompatible with cerebral function before the rise of  $P_{CO_2}$  becomes unbearable. Exercise seems to increase the subject's tolerance of hypercapnia. The  $P_{CO_2}$  in the alveolae is higher at the breaking point when the subject held his breath during exercise than when respiration was suspended during rest. This displacement of the breaking point curve increases the likelihood of hypoxia. Loss of consciousness in hypoxia occurs with little specific warning. Between the time of loss of consciousness and final collapse the subject may continue his previous activity. Similar data are analyzed in Craig's paper (2388) published in 1961.

Bradycardia is a response to apneic diving which man shares with many other species. Craig (2390) 1963, observed slowing of the heart rate during diving in children as well as in adults and found that this was as prominent in poor swimmers as in those subjects who were familiar with the water. The response was independent of depth down to 27 meters, but could not be produced by simulated dives in a decompression chamber. Diving in water implies several maneuvers, some of which were investigated during breath holding. It was observed that the tachycardia produced by breath holding at different valsalva pressures was proportional to the increase of intrathoracic pressure. At equal pressures the tachycardia was less when the subject was in water than when in air. Other maneuvers which increased venous return at the beginning of the breath hold produced a bradycardia during the

apnea, and conversely when venous return was impaired there was a tachycardia. The hypothesis is presented that diving bradycardia in man might be explainable in terms of already known physiological mechanisms. In a study of breath holding after exercise, Craig and Cain (2391) 1957, measured breath holding time after five grades of work in a group of 12 men. An average of 1.4 seconds elapsed between the signal (given without warning) and the cessation of inhalation. During this time the volume inhaled varied with the phase of the breathing cycle in which the signal was given. It was greatest when the signal was given in the quarter cycles immediately before and after the beginning of inspiration. Since breath holding time was unaffected by the phasing of the signal it is thought that the volume of the lung was adjusted to enable the breath holder to begin with a full lung (full in the sense of a full tidal volume characteristic of the previous grade of work). The mean breath holding time decreased from 25.8 seconds after the lowest grade of work to 5.8 seconds after the highest. It was proposed that the stimulus to breathe at the end of the hold was the same after all grades of work. The stimulus was evaluated in terms of a rate of accumulation of a chemical stimulating condition proportional to the previous respiratory minute volume multiplied by the length of the hold and divided by the estimated volume of the lungs during the hold. Calculated in this way the value assigned to the stimulus varied from 1.0 to 1.3 among the grades of previous work. In half of the trials alternating gasps and holds were continued after the initial hold for a total of 30 seconds. The succeeding breath holding times were essentially of the same length as the first. The volume of the succeeding gasps varied only slightly with the previous grade of work.

Fowler (2400) 1953, has reported an attempt to evaluate the mechanical factors which are determinants of the breaking point of voluntary breath holding.

Olsen, Fanestil and Scholander (2412) 1962, carried out investigations of the effects of breath holding on cardiac rate and rhythm in man. The subjects held their breath in a wooden tank lying prone underwater. The periods of apnea were the longest with simple breath hold-



ing without exercise and without preceding hyperventilation. There was a consequent bradycardia which was not prevented by exercise. Out of 64 periods no changes in cardiac rhythm were seen in 10 out of 15 periods of simple breath holding. The most frequent rhythm change was a decrease in the amplitude of the P wave without any alteration in the P-Q interval. This was usually preceded by an abrupt decrease in the rate. The next most common change consisted of abnormal rhythms arising in the A-V node or common bundle of His, sometimes preceded by A-V dissociation. This appeared at an average heart rate of 54 beats per minute. There were idioventricular rhythms and a sinus arrest in three subjects at rates of 37, 43 and 30 beats per minute. Supraventricular premature beats were observed during dives and during recovery. Progressive increase in the amplitude of the T wave was observed during breath holding. During recovery there was prompt return to sinus rhythm; the return to normal T waves was more gradual. Sinus tachycardia and arrhythmia with premature beats of atrial nodal or ventricular origin were common during the first 30 seconds of breathing following the test. The development of bradycardia during underwater swimming is apparently a prerequisite to safe adaptation. In a study of effects of apneic underwater diving on blood gases, lactate and pressure in man, Olsen, Fanestil and Scholander (2413) 1962, directed five men (32-54 years of age) of outstanding diving ability in performing apneic underwater dives in a specially fitted tank. A forearm was held out of water in some studies; in others the head and shoulders were out of water. The water temperature ranged from 26 to 37°C. Exercise dives consisted of pedaling 76 strokes per minute with 12-23 Kg. weights. The divers hyperventilated to extreme degrees of hypocapnia before submerging, and their arterial blood carbon dioxide tensions rarely rose above normal levels during a dive. Arterial blood oxygen content was 15.5 volumes percent or above at the end of two 3-minute rest dives and of three 1.5 minute exercise dives. Blood lactate concentrations increased during the latter half of exercise dives and reached peak values after surfacing. An initial rise in blood pressure was followed by a drop which was maximal at five

seconds and then rose and continued to the end of the dive. The blood pressure became irregular at the end of the dive coinciding with the increased muscular activity. A transient rise in heart rate coincidental with a fall in blood pressure was followed by a progressively irregular fall in pressure. The rate of blood pressure rise was greater during a dive in water of 26°C. than with breath holding by the same subject out of water. Elsner (2397) 1963, has experimentally studied limb blood flow in man during breath holding dives. The circulatory responses to diving in animals are known to include bradycardia and general peripheral and visceral ischemia with little change in blood pressure. In Elsner's study a search was made for peripheral ischemic reactions during diving. Young adult male subjects were used in experiments in which heart rate and calf blood flow were measured in the prone position during simple breath holding and during dives which consisted of face immersion in water. Typical apneic periods lasted one minute. Limb blood flow was measured plethysmographically using the Whitney gauge method. All subjects had bradycardia and decreased calf blood flow during dives. Both heart rate and blood flow were reduced more with face immersion than by breath holding alone. The response was unrelated to diving experience and it was variable, ranging from slight to extreme. A heart rate of 12 per minute was recorded in one subject; another's blood flow was undetectable during the dive, although he had profuse flow both before and after it. Tachycardia and hyperemia caused by limb exercise were also reduced by diving.

For further information on breath holding the reader is referred to a symposium on this subject held at the International Physiological Congress in Japan in 1966 and as of this writing still unpublished.

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## B. ESCAPE PROCEDURES

It is strongly suggested that readers refer to Volume II of this Sourcebook (pages 251-254) for two dramatic accounts of actual escape attempts. The first disaster occurred off Formosa in 1944 when the U.S.S. *Tang* was sunk by its own torpedo. The second catastrophe concerns re-



ports of survivors from the German submarine *U-1195* sunk in April 1945 in the English channel. Both of these reports provide valuable information.

A general discussion of submarine escape and free ascent has been given by Miles (2430) 1962. To reach the surface the submariner must first be compressed to the pressure of the water surrounding the submarine and then be decompressed as he rises through the water. It is quite impossible for any hatch in a submarine to be opened from within until the pressure inside has been raised to that outside. Even at a shallow depth of 33 feet the hatches are kept shut by a pressure of about 7 tons. A history of submarine escape is outlined and a report of an Admiralty Committee on Submarine Escape stated as follows: 1) The major hazard is within the submarine prior to ascent. About 75 percent of all submarine escape casualties occurred during the period of flooding. 2) During World War II as many men made an escape ascent without breathing apparatus as did with it.

Escape procedures must fall into two major groups: 1) those in which survivors remain at atmospheric pressure throughout (as in the situation in which the escape bell can be lowered from the surface and fastened to the escape hatch of the submarine). 2) situations in which the pressure in the submarine must be raised to that of the surrounding water so as to allow the survivors to open the hatch and then make their ascent. Both methods are in use today. There are of course definite limitations to the use of the bell. Direct rescue with the bell depends upon the early arrival of highly technical surface assistance. A limitation to such methods is that frequently much time will elapse before rescue ships can reach the area and fasten the bell upon the submarine or that the submarine may be in a position which makes such an operation difficult or impossible. The state of the sea further complicates or prevents the above maneuvers. With nuclear powered submarines a situation may well arise where such a vessel although disabled and unable to leave the bottom may maintain its domestic services and air purification facilities for weeks. This opens up possibilities of "unhurried" salvage and improves chances of obtaining ideal conditions for the use of the

rescue chamber. The rescue chamber or bell is standard equipment in the U.S. Navy and immense organization is demanded to maintain it. In practice the chamber is carried by rescue vessels which have trained and experienced divers on board. The pressure equalization method of escape depends on the man's ability to leave the submarine on his own. For this it is necessary for the pressure within to be raised to that outside before any hatch can be opened. Four stages must be considered: 1) within the submarine before flooding and pressure equalization is commenced; 2) the period of equalization; 3) the ascent and 4) survival on the surface.

Miles has stated that what happens during the pre-flooding period depends upon conditions within the hull just after the accident. If there has been structural damage and general flooding, escape of toxic fumes or other immediate emergency, escape must be precipitous with the object of abandoning the craft as quickly as possible. Under other circumstances the damage may be isolated and the men alive and secure in undamaged compartments. Here consideration must be given to the number of men, the condition of the atmosphere and so on.

During the period of pressure equalization an important hazard may arise from the increase in pressure which in turn can produce lethal pressures of carbon dioxide and other impurities. The effects of a continued stay at pressure must also be considered. The longer the time of exposure to pressure the greater will be the danger of decompression sickness on ascent. If the submarine is deeper than 145 feet there will be risk of decompression sickness if air is breathed. At 200 feet the safe time for exposure if bends are to be avoided is about six minutes, and at 300 feet it is three minutes. The pressure being equalized, the hatches can be opened and no time is lost by the men in escaping either from the compartment or the chamber. Miles has suggested that the outflow of air helps to prevent an accumulation of carbon dioxide which might otherwise bring breath holding to an end and at the same time there is sufficient oxygen partial pressure to maintain consciousness. The increase in the rate of air escape can be seen if a man is followed up through the water trailed by a gentle stream of bubbles, beginning with a





may express fear of death. These initial features of the embolism may come on during a thoracic procedure, as stated. Following the early warning symptoms there is usually loss of consciousness, the duration of which is variable. Some patients retain consciousness but are disoriented. Convulsions occur in somewhat less than half the cases and may be localized or general, tonic or clonic, or both of the latter in sequence. Localized neurological manifestations are noted following return of consciousness, although they may appear earlier. These include hemiplegia, hemiparesis, hemianesthesia, monoplegia, hemianopsia, nystagmus and strabismus. Frequently these signs disappear within a few hours or days but cases have been recorded in which hemiparesis persisted for as long as four months. Blindness may occur also, and may be complete even in patients who have not temporarily lost consciousness. This manifestation may persist for several days. Pupils are usually dilated, and sometimes widely so, but occasionally they are constricted. Cyanosis is noted in the majority of instances. The respiratory rate is generally slowed, and sometimes Cheyne-Stokes breathing is observed. Manifestations of peripheral vascular collapse are frequent, and may be severe even in those who later recover. Following recovery from the acute episode, should the patient be so fortunate, pain in the chest referred to the precordial or substernal area, is a frequent complaint and may be accompanied by considerable dyspnea. Electrocardiographic evidence of myocardial infarction has been observed. Nausea and vomiting may be troublesome complaints and persist for hours or days.

Liebow, Stark, Vogel and Schaefer (2465, 2466) 1959 and 1960, have presented details of two casualties encountered in submarine escape training and have considered the role of intrapulmonary air trapping in each case. One patient survived and the other died. In the fatal case a broncholith of tuberculous origin acted as a ballvalve within a subsegmental bronchus. In the other patient who survived, the mechanism of the bronchial obstruction was not apparent, but a large bulla was demonstrated roentgenographically after decompression. This was almost entirely absorbed within 36 hours after the patient's return to atmospheric pressure. The

problem of detecting persons potentially predisposed to involuntary air trapping when breathing air at supra-atmospheric pressure and subjected to the stress of rapid decompression is an important one. Individuals with obstructive pulmonary emphysema, with significant pulmonary calcification (in whom broncholiths may exist), or those with evidence of chronic respiratory disease, should be eliminated from submarine escape training. As shown in the case of the second patient, even careful radiographic and physiologic studies may fail to demonstrate air trapping under ordinary atmospheric pressure with the methods now available. Again it should be stated that facilities for immediate, rapid recompression should be available because at present this method offers the only means of therapy, the efficacy of which has been attested to under the practical conditions of submarine escape training.

For two other papers reporting case studies, reference is made to Collins (2440) 1963, and Miasnikov and Mashkov (2472) 1961.

Further references on the treatment of air embolism may be cited: Clemmedson and Hultman (2438) 1954, have discussed recompression of animals subjected to air blast injury. The occurrence of air embolism and the cause of death in such injuries was studied by these authors in anesthetized rabbits exposed to high explosive blasts in an open field and in a specially constructed detonation chamber. Intravascular air was found in a fairly high number of the animals that died within 15–20 minutes after the exposure. Air embolism was rare in animals dying later on. By recompressing the animals to four atmospheres gage pressure immediately after the detonation, it was possible to reduce considerably the occurrence of intravascular air bubbles. Peter and Grüning (2476) 1954, point out that the pathological-anatomical findings in arterial air embolism are similar to those existing in caisson disease and recommends recompression as the treatment procedure. The authors reported the use of this treatment in guinea pigs in which large arterial emboli had been produced. Moretti (2474) 1963, also calls attention to immediate recompression, as well as placing the patient in a position with the feet elevated and the head lower than the rest of

the body. The patient should be placed on his left side. Musgrove and MacQuigg (2475) 1952, report the case of severe air embolism successfully treated by turning the patient to the left lateral position.

The prevention of gas embolism in escape by any other ascent from depth rests essentially upon training of personnel to achieve an effective appropriately controlled exhalation of air from the lungs during the ascent. Also, careful physical examination to rule out so far as possible any pulmonary condition that would impede this is required. Various investigators have demonstrated that binders around the chest and abdomen prevent overdistention of the lungs and keep the transpulmonic pressure from reaching a critical value. Schaefer, McNulty and Carey (2478) 1957, for example, have conducted such studies on dogs. These animals were decompressed within two minutes during which time the trachea was closed from a pressure equivalent of 100 or 200 feet to sea level. Recordings of pressure were taken from the abdominal aorta, the inferior cava, the left atrium, the pulmonary artery and trachea, the intrapleural space and abdominal cavity. All dogs were prepared by operation two to four weeks before the experiments. The pressure gradient between the intratracheal and intrapleural pressure (transpulmonic pressure) was found to be the decisive factor in producing embolism. The critical level of transpulmonic pressure was 60–70 mm. Hg. It was found that binders around the chest and abdomen did act effectively. However, abdominal binders alone failed to give protection against air embolism. Similar studies were also reported by Schaefer, McNulty, Carey and Liebow (2479) 1958. When unprotected dogs were decompressed from 100 or 200 feet equivalent depth with the trachea closed, there developed pulmonary interstitial emphysema and air embolism, probably via the pulmonary veins when intratracheal pressure reached a critical level of approximately 80 mm. Hg. The lungs became markedly distended by entrapped air expanding as the ambient pressure was reduced. The systemic aortic pressure fell in consequence of compression of the postarterial vessels in the lungs, indicated by a higher gradient between pulmonary arterial and left atrial pressures. Interstitial

emphysema and air embolism could be prevented as indicated above, by the application of thoraco-abdominal binders, despite a rise in intratracheal pressure to levels of 180 mm. Hg or more. The effects of the binders were: a) to prevent overdistention of the lung as indicated by the small difference between the intratracheal and intrapleural pressures; b) to keep at a lower level the pressure gradient between the respiratory passages and the pulmonary veins and left atrium; and c) to maintain the systemic aortic pressure in part, at least in consequence of a low transcapillary pressure gradient. These observations suggested to the authors the possible utility of compressive garments of the "G-suit" type in escape procedures. Malhotra and Wright (2469) 1960, examined the intratracheal pressures at which pulmonary barotrauma occurs in five fresh cadavers, one unbound, one with abdominal binding and three with both chest and abdomen bound. Autopsy examination was done subsequently to determine the site and nature of injuries. It was determined that in the unbound subject and in the subject with abdominal binding the pressure at which trauma occurred was approximately the same, namely 80 and 93 mm. Hg respectively. On the other hand in those whose chest and abdomen were both bound the pressures were very much higher, namely 190 mm. Hg in two cases, and 133 mm. Hg in the third subject. In the unbound cadaver rupture of the visceral pleura was seen where basal pleural adhesions were present. In the remaining four cases pulmonary interstitial emphysema resulted. It was concluded by the authors that rupture of the lung occurs due to overexpansion and that the presence of basal adhesions predisposes to this form of trauma. In cadavers the abdominal binder protects against rupture of the basal part of the lung but not against pulmonary interstitial emphysema. Binding of both the chest and the abdomen was found to be more effective. Malhotra and Wright (2470) 1961, have reported that arterial air embolism is rarely seen in Naval operations, except during diving, submarine escape training or during explosive decompression. The authors studied the effects of decompression of tracheotomized rabbits. The animals were taken to a simulated depth of 100 feet of water in a pressure chamber



and then decompressed, the trachea being closed at a depth of 60 feet until the surface was reached. The principal injuries in ten animals were air embolism, pneumothorax and interstitial emphysema. When pneumothorax was present, the quantity of air in blood vessels was smaller or absent altogether. Air appeared in the circulation only after intratracheal pressure was allowed to return to ambient pressure. Manual squeezing of the chest or applying abdominal binders prior to clamping the trachea were both found to be effective in preventing these injuries in a further series of ten rabbits. Squeezing the chest reduced the volume of air in the lungs nearly to residual. The binder not only reduced the initial lung volume by raising the diaphragm but also provided support to the lungs during decompression. In a few human trials subjects ascending from a depth of 100 feet found the ascent more comfortable when wearing binders than without them.

A number of experimental studies of air embolism may be referred to. Geoghegan and Lam (2451) 1953, concluded in dogs that air reaching the left heart is capable of causing almost instant death by filling the coronary arteries. Air in the cerebral arteries of dogs given respiration does not result in immediate death but in critical amounts does produce severe brain damage. The presence of air in the coronary arteries does not necessarily constitute an irreversible lesion, since a high percentage of hearts can be completely resuscitated following injection of an otherwise fatal dose of air into the left ventricle if a high pressure in the coronary arteries is maintained to force air through to the venous side. Harvey and Schilling (2453) 1954, have studied the relationship between lung pressures and volumes in traumatic air embolism. The purpose of their study was to determine the conditions at which lung rupture and air embolism occur. The unopened thoraces of nembutalized dogs were expanded after occluding the trachea by reducing the air pressure in the chamber in which the dogs were placed to a predetermined value (within 2 seconds). The functional residual volume was determined previously by decompression at the end expiratory position with the trachea open to a spirometer. Subsequently measured amounts of air were added to

the initial volume. The animal was then decompressed from ground level to 250 mm. Hg with closed airways and kept there from 15-20 seconds before return to ground level. Tracheal, intrapleural, pulmonary arterial and venous, femoral, arterial and chamber pressure were recorded using strain gauges. Criteria of lung rupture and air embolism used were a fall in tracheal pressure, reduction of tracheal pressure below control values when the chamber was brought back to ambient pressure, a change in electrical conductance between an electrode catheter in the pulmonary vein and the tissues, and lung hemorrhage. Control measurements were made by decompressing the dog without tracheal occlusion. It was found that lung rupture and air embolism first occurred at lung volumes approximately three times the functional residual volume. A large pressure gradient between the air passages and the pulmonary vein was found to develop with lung distention. Reference may be also made to Fries, Levowitz, Adler, Cook, Karlson and Dennis (2450) 1957, who have reported studies of experimental cerebral gas embolism. Studies of air embolism during decompression and its prevention in animals by Malhotra (2468) 1959, should also be consulted. Reference should also be made to a report by Eiseman, Baxter and Prachuabmoh (2448) 1959. These authors have drawn attention to surface tension-reducing substances in the management of experimental coronary air embolism. It was found that the introduction of surface tension depressants into the left ventricle of dogs simultaneously with injection of an otherwise lethal dose of air decreased the mortality approximately 50 percent.

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#### D. UNDERWATER BLAST INJURIES

The interest in the hazard of underwater blast has escalated with the greater use of underwater swimmers for underwater demolition work and for other military operations in forward areas. The interest also extends to survivors of disaster at sea during wartime. In waters where detonation of armed charges, mines, etc. may occur.

It has been found (2498) that 500 psi is sufficient to cause injury to the lungs and intestines, and over 2000 psi is fatal. The more serious initial compression wave produced by violent liberation and expansion of gas during the detonation is followed by a low pressure wave resulting from the subsequent collapse of the mass of expanded gas. Injury takes the form of shredding of tissues constituting the walls of spaces (or nearby tissues) due to differences in pressure which develop from differences in rate of pressure transmission in non-compressible tissues and airspaces. Slow detonation, although of longer maximum pressure, lasts longer and does more damage at long range. The incompressible nature of water causes transmission of the blast with greater force than in air. Parts of the body out of water are unaffected by an underwater blast and submersion protects against air or surface blasts. Reflections of pressure from a hard bottom add to the damage. The added bulk of most protective clothing makes its use generally impractical. Some protection is offered by floating with the thicker tissues of the back between the vulnerable organs and the explosion source. Bebb (2489) 1953, has also discussed interposing materials between the underwater explosive and the body tissue. The factors determining the degree of injury in underwater blast (2497) are: a) the proximity to the blast, b) the size and type of explosion, c) the medium through which the force is transmitted, d) the degree of submersion of the diver or person, and e) the protection worn by the diver. The chest and abdomen are the most common sites of injury. The brain may be damaged if the head is submerged at the time of blast. Bruising and laceration of the skin is not seen even though underlying organs may be severely damaged. Skeletal injuries are uncommon.

Clemedson and Hultman (2438) 1954, have carried out a study on the occurrence of air embolism and the cause of death in blast injury in rabbits. This paper has been referred to above. In these animals exposure to high explosives in air resulted in air embolism as well as severe damage to the myocardium. This latter was considered due either to the air embolism or to mechanical lesions of the heart muscle. Clemedson (2493) 1956, has pointed out that

underwater blast pressures of over 200-300 psi will cause lung injuries in rabbits. Intestinal perforations may also occur under these conditions. Immersed persons exposed to blast pressures in excess of 500 psi will sustain lethal injuries from ruptures of pulmonary vessels or of the intestine. In a study on the relation between the duration of a shock wave and the severity of the blast injury produced by it, Celander, Clemedson, Ericksson and Hultman (2491) 1955, found in mice that the longer the duration of the shock the more severe was the inflicted injury. Of the two factors, maximum pressure and duration, the first seems most important as far as injurious effects are concerned. Of interest are Clemedson's findings (2492) in rabbits that there is no correlation between the respiratory phase and the lung damage. Exposure to a shock wave of long duration causes an expulsion of air from the lungs and is seen even if the lungs are in maximal expiration. A shock of a short duration causes a slight or no expulsion of air.

The area of protection of personnel against underwater explosion is under investigation and various protective garments are being studied. For example, House, Prenderville, Wilson, Wilson and Bebb (2496) 1955, have investigated suits using fiberglass. Kapok and other substances have also been studied; these garments have been designed for the chest and abdomen and also headaddresses have been studied to absorb shock. One of the main problems in the practical application of such studies is that of designing suits that can be worn under ordinary operation and also be effective during emergencies.

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### E. DROWNING

Most of the fatal casualties among underwater swimmers have been due to drowning. The papers quoted in this section do not constitute a comprehensive collection of the literature on drowning as a whole but are representative and are chosen because of their particular relevance to resuscitation and survival problems.

Donald (2501) 1955, has distinguished between fresh water drowning and salt water drowning. In the former there is absorption of water across the capillary membrane which can be estimated by the degree of hemodilution or by measuring the levels of blood concentration of tracer substances placed in the drowning fluid. It has been shown that an amount of water equivalent to 60-150 percent of the blood volume can enter the circulation within a few minutes. The rate of dilution is quite fantastic. The hemodilution is followed by hemolysis with a concomitant gain in potassium ions; therefore the potassium/sodium ratio is increased. This disturbance in electrolyte ratios is more dangerous than the overall changes in tonicity. Within a few minutes ventricular fibrillation may begin; great overloading of the increased blood volume also contributes, along with the anoxemia. There is also a pulmonary vasoconstriction. After death the right ventricle is distended and the left almost empty and fully contracted. The reduced blood pressure along with the reduced cardiac output leads to central nervous system hypoxia and finally anoxia. Respiratory failure occurs about the same time as the ventricular fibrillation.



In salt water drowning there is movement of water out of the blood into the lungs with a resulting hemoconcentration. There is no hemolysis or change in the potassium/sodium ratio, and ventricular fibrillation does not occur. The heart fails gradually within five to eight minutes. If the systolic blood pressure remains above 115 mm. Hg, resuscitation is almost always successful, even though the diastolic pressure may be extremely low. There is evidence of severe pulmonary edema with plasma exudation into the alveoli of both the salt water and fresh water drowned animals. The resultant protein content of the lung fluids is partly responsible for the tenacious froth encountered in the air passages. The stomach may contain very large amounts of the drowning fluid owing to reflex swallowing, and there may be evidence of the stomach contents in the air passages due to agonal vomiting. Survival is practically nonexistent without resuscitation when the blood pressure has fallen precipitously and this is probably due to the ventricular fibrillation.

Exercise before drowning seems to lower the survival rate. In surviving human beings mild pulmonary edema is usually found in the case of both salt and fresh water drowning. This is thought to be due primarily to anoxic effects and central nervous system effects rather than due to aspiration of water. There are no signs of renal damage. If irreversible circulatory failure has occurred artificial respiration cannot succeed. If only respiratory failure has occurred, then only seconds may remain before circulatory failure supervenes. Not a second, literally, can be wasted in initiating resuscitating measures. Artificial respiration must be started even at the risk of other injuries. No time should be wasted in clearing airways, loosening clothing, feeling the pulse, etc. If someone else is available they can handle these duties. Even a small amount of air in the first few seconds may accomplish what 100 percent oxygen and large pulmonary ventilation may fail to do after 10–20 seconds. Sometimes a person with medical knowledge may constitute a threat in getting a detailed clinical examination while artificial pulmonary ventilation should be going on.

Selected case reports are given in the following papers: Haddy and Disenhouse (2505) 1954,

discuss a 10 year old girl who had been immersed for two to three minutes in fresh water. The child was extremely disoriented and agitated and showed swimming movements of the extremities, hyperventilation and cyanosis. There was bloody mucous in the pharynx, but no sign of injury. Many fine moist rales were heard throughout both lung fields. Fifty percent oxygen was administered first in an oxygen tent and then under positive pressure for 20 minute intervals, alternating with 40 minute intervals at atmospheric pressure. After three hours there was a definite increase in pulmonary edema; seven hours later there was much improvement. On the third day the oxygen tent only was used for a few hours and then discontinued. There was a continuation of recovery with no further difficulty after the sixth day. Hack (2511) 1959, reported the case of a chief returning to a submarine who fell on the saddle tank and was immersed in the water for 30–60 seconds. He recovered consciousness within a few minutes and was taken to the sick bay. There he vomited twice. He was very excited and would not lie still. The patient could not remember anything about the accident. His pulse was 80 and there was good volume. There was no cyanosis; within the chest numerous crepitations were heard all over. The pupils were equal and reacted sluggishly to light; the knee jerks were also sluggish. The patient was discharged to a hospital ashore with possible skull fracture, and died 2.5 hours later. The lungs on autopsy were congested and waterlogged and the cut surfaces exuded fluid. The right auricle and ventricle were dilated and contained a clot. The stomach contained 450 cc. of green fluid mixed with a few food particles. There was no evidence of skull fracture; the brain exhibited moderate congestion without evidence of brain damage. Microscopically there was intra-alveolar edema and striking congestion of the alveolar capillaries. There was moderate desquamation of the alveolar lining cells, and there was shedding of the epithelial layers in the bronchioles. The microscopic appearances in the bronchi and lungs, particularly the presence of such a well-marked reaction in the bronchioles occurring so quickly after immersion, reinforce the impression that some irritant in addition to sea water was inhaled. The water around the

submarine had a film of oil which may have been contaminated by detergent "scum" from the ship's laundry.

Courville (2500) 1960, has reported the case of a patient who survived for 19 days after prolonged immersion. A young man of 21 years of age was pulled out of a swimming pool in an unconscious state and was resuscitated by a rescue squad. He had been practicing breath holding and had evidently inhaled some water accidentally. He failed to regain consciousness after spontaneous respiration and cardiac action had been restored. The patient developed a typical decorticate state during the survival period. The brain showed histological signs of cerebral anoxia. Kvittingen and Naess (2513) 1963, have pointed out that survival after drowning in fresh water is rare when submersion has lasted so long that aspiration of water has led to hemolysis and hemoglobinuria and cardiac arrest has also occurred. A case is reported of a five year old boy who drowned in ice cold water having been immersed for 22 minutes. The patient was successfully resuscitated by external cardiac compression which was carried out for two hours before spontaneous cardiac contractions were restored. The hemolysis and hemoglobinuria were treated with an exchange transfusion of 3000 cc. Apart from a brief return to consciousness on the tenth day, the boy was unconscious for about six weeks. Air encephalograms taken six weeks after the accident showed severe dilatation of all cerebral ventricles. In spite of all this the patient recovered with little if any neurological and intellectual damage. Air encephalograms taken six months after the accident showed that dilatation of the cerebral ventricles had decreased. The authors suggested that cooling of the child's body during treatment and as he hung onto the ice had played an important part in the successful outcome.

King and Webster (2512) 1964, have described a case of a German seaman, 21 years of age, who was painting the side of a ship and fell 20 feet, striking first the wharf and then the water. He was recovered by a skin diver who rescued him from the river bottom in 30 feet of water. Immersion lasted at least 17 minutes. The patient recovered from cardiac arrest and electrolyte disturbances but there was absence of gross

hemolysis or pulmonary edema. The patient made a dramatic recovery. Immediate mouth to mouth resuscitation was used and the authors stress the importance of this and its continuation in even apparently hopeless cases.

Gordon, Raymon and Ivy (2504) 1954, have reported drowning phenomena in various species of animals. In a large number of animal species submersion in fresh water resulted in two general types of blood pressure response: a) a precipitous fall to zero within one to three minutes, or b) a gradual fall to zero during two to five minutes. All animals showing the former response had simultaneous ventricular fibrillation. All horses, cows and pigs showed precipitous blood pressure drop with permanent ventricular fibrillation. Most of the dogs showed this response but only a few of the sheep and goats. Cats, rabbits and monkeys all exhibited a gradual fall in blood pressure without permanent ventricular fibrillation, however, four cats, three monkeys and one rabbit had transient episodes of ventricular fibrillation with spontaneous recovery. Data were also obtained on serum hemoglobin, sodium, potassium, calcium and chlorides, before and after fresh water submersion. In general the hemolysis was greater in those animals of each species that exhibited either transient or permanent ventricular fibrillation. The serum ionic determinations revealed a significant rise in potassium and decrease in sodium, calcium and chlorides, in all species. The mechanism of ventricular fibrillation during fresh water drowning is stated by the authors to be related to: a) ionic imbalances resulting from anoxia, hemodilution, hemolysis and sympatho-adreno-hepatic stress; b) increased intravascular clotting; and c) animal size.

Foden, Stemler, Rockhold and Hiestand (2503) 1952, have indicated that body temperature is a major factor in survival from drowning. In an investigation of the effect of altering the body temperature of mice on survival to drowning, a significant linear relationship appeared when body temperatures were plotted against survival time, as measured by the final gasp. Various agents, as well as mechanical means of chilling, in ice baths and heating with infra-red radiation were used to alter internal temperatures. Substances which markedly low-



ered temperature always caused an increase in survival time. Those which increased temperature or metabolic activity caused a decrease in survival. The most pronounced increase in survival occurred with chilling, previous exposure to oxygen, injections of ethyl alcohol, India ink, and powdered charcoal. Prolongation to a lesser degree was shown by ACTH, cortisone, thiouracil and gum acacia. A decrease in survival time followed heating, exposure to cold for 48 hours, dinitrophenol and, to a lesser degree, throxin. Other substances tested such as cocaine and histamine showed no appreciable effect. Exercise (swimming in water for periods of 15 minutes to one hour) increased survival time by over 20 percent. Starvation for 48 hours reduced survival time only slightly. All animals were males.

Rath (2516) 1953, has reported a case of a 15 year old boy exhibiting hemoglobinemia and hemoglobinuria following incomplete drowning. The patient recovered and four years later was still asymptomatic. There was no evidence that the hemoglobinemia was caused by a mechanism other than intravascular hemolysis from fresh water entering the general circulation. In experimental studies to localize the point of entrance into the circulation, a dog was anesthetized and 620 cc. of distilled water were injected over a period of 95 minutes into the trachea with no evidence of hemoglobinuria. Nor was there any evidence of hemoglobinuria when 1800 cc. were injected over 45 minutes in the same dog. When the tracheal cannula was tied in place to prevent coughing up water and swallowing, 1000 cc. were injected over a period of 65 minutes. One hundred and ten cc. and 128 cc. of the water had entered the circulation through the lungs at 20 and 65 minutes respectively. The degree of hemolysis was less than previously reported by others. There was no hemoglobin in the urine. The animal expired.

Redding, Voigt and Safar (2518, 2519) 1960, have carried out some studies on dogs in which drowning was treated with intermittent positive pressure breathing. These dog experiments were designed to simulate the condition of human victims of submersion who seemed first to develop laryngospasm, followed by flooding of the lungs. The tracheal tube of lightly anesthetized dogs

was clamped until the onset of apnea. The lungs were then flooded for 30 seconds with fresh water or sea water, or apnea was permitted to continue for a comparable period without flooding. Resuscitation was attempted with intermittent positive pressure breathing utilizing room air. All control dogs (obstructive asphyxia without flooding) survived. Fresh water drowning caused mild arterial hypotension, a severe rise in venous pressure and bradycardia, followed by sudden ventricular fibrillation within 1-4 minutes in spite of intermittent positive pressure breathing. Sea water drowning caused severe arterial hypotension, a slight rise in venous pressure and bradycardia. Intermittent positive pressure breathing led to partial reoxygenation and partial restoration of circulation. When intermittent positive pressure breathing was discontinued all dogs started to breathe spontaneously, but within a few minutes developed asystole with pulmonary edema.

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# Protection and Preservation of Personnel

## I. GENERAL STUDIES

The ability to withstand exposure to severe stress is never an adequate selection procedure for submariners or divers. Superimposed upon a realistic and efficient selection program must be efforts to protect personnel from intolerable stresses by attention to habitability, food and water supply, and special equipment and devices. In all procedures and plans for protection and preservation of personnel, it must be borne in mind that the submarine is a fighting ship. The effective fighting power of the submarine is the primary consideration, and all matters of protection and comfort of personnel are important in the degree to which they contribute to this.

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## II. VENTILATION AND AIR CONDITIONING

### A. GENERAL STUDIES

Modern advances in the engineering of submarines have largely solved many of the most harassing problems of conditioning and habitability. In many ways the atmosphere of the modern nuclear-powered submarine is cleaner than that in many American cities. The problems that still remain in the air conditioning of submarines are the removal of trace contaminants and odors from the sanitary tanks. The references included in this section will permit the reader to follow the course of some of these developments.

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## B. PREVENTION OF ATMOSPHERIC POLLUTION

Prevention of atmospheric pollution in the submarine rests upon meticulous and successful screening of all potential atmospheric pollutants that may be brought aboard or used by personnel or exist as structural parts of equipment. In the reference list that follows the reader will find a rich source of papers dealing with various contaminants, their detection, screening and effects on personnel.

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- C. ELIMINATION OF DUST, GASES, FUMES AND ODORS FROM AIR**
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2599. Thomas, F. S. The elimination of the oxidizable contaminants in submarine atmospheres by combustion. pp. 55-66 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by R. R. Miller and V. R. Piatt. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5465*, April 1960, 167 pp.

2600. Thomas, F. S. hTe CO/H<sub>2</sub> burner, pp. 103-105 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by V. R. Piatt and E. A. Ramskill. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5630*, July 1961, 134 pp.

2601. Tohmas, F. S. The CO/H<sub>2</sub> burners. pp. 83-85 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5814*, August 1962, 97 pp.

#### D. PHOTOSYNTHETIC GAS PRODUCTION AND UTILIZATION

Algae as a source of oxygen for nuclear submarines have been considered and this constitutes a lively subject of research concern.

2602. Hannan, P. J. Algae in a photosynthetic gas exchanger. pp. 18-28 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by V. R. Piatt and E. A. Ramskill. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5630*, July 1961, 134 pp.

2602a. Hannan, P. J., C. Patouillet and R. Shuler. Studies of oxygen production by mass culture of algae. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5689*, December 1961, 23 pp.

2603. Hannan, P. J., R. L. Shuler and C. Patouillet. Algae in a photosynthetic gas exchanger. pp. 21-34 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by V. R. Piatt and J. C. White. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5814*, August 1962, 97 pp.

2604. Hannan, P. J., R. L. Shuler and C. Patouillet. Algae as a source of oxygen for nuclear submarines. pp. 10-24 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by H. W. Carhart and V. R. Piatt. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 6053*, December 1963, 65 pp.

2605. Leonard, J. M. Algae and submarine habitability — an appraisal. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5182*, August 1958, 8 pp.

#### E. CARBON DIOXIDE ABSORPTION

Only two of the following references will be specifically discussed. Duffner (2611) 1957, has studied canister design criteria of carbon dioxide removal from SCUBA. An empirical set of design criteria for a SCUBA carbon dioxide removal canister were derived from data obtained by a review of the pertinent literature. Such a device, presuming satisfactory performance for 180 minutes at 30 feet, and for 30 minutes at 180 feet, must be capable of absorbing a minimum of 600 grams of carbon dioxide. It must also remove 75-80 percent of the carbon dioxide from a mixture containing 0.5 to 2.0 percent carbon dioxide passing through it at a velocity of 55-90 liters per minute. It must remove 70-75 percent of the carbon dioxide from a mixture containing 1.0 to 2.5 percent carbon dioxide passing through it at a velocity of 125-200 liters per minute. The breathing resistance must not exceed 1.5 cm. of water per liter per second, and the inter-granular space must be at least 3.5 liters.

McConnaughey and Crofford (2620) 1956, have conducted tests of the Girdler carbon dioxide scrubber installed on the *USS Nautilus*. The project was to evaluate suggested changes in



the plant operation. The purpose was to increase the capacity above that attainable with the specified absorbent solution mixture of 2.5 normal diethyleneglycolamine (DEGA) and mehtyl-diethanolamine (MDA). Studies were made with 4.5 normal monoethanolamine (MEA) at 1.5 percent carbon dioxide; with 3.5 normal diethanolamine (DEA) at 1.5 percent carbon dioxide; and with 4.5 normal MEA at 3 percent carbon dioxide. It was found that MEA at both carbon dioxide concentrations showed an increased removal rate, the plant capacity at 1.5 percent carbon dioxide being 10 to 10.5 pounds per hour, or about 70 percent greater than that obtained in previous dockside runs using the DEGA-MDA mixture. The DEA run removed around 8 pounds per hour at 1.5 percent carbon dioxide. No detectable amine vapor or fogs were found in the atmosphere although excessive losses of amines occurred on the MEA runs. This loss is most likely due, according to the authors, to leakage rather than to vapor losses or to destruction of the amines.

Since the reference lists for the present Volumes were tabulated and serialized, three excellent research reports have appeared and are referred to in the text. All of these reports emerged from U.S. Navy Experimental Diving Unit, U.S. Naval Station, Washington Navy Yard Annex, Washington, D.C. The first is a study by M. W. Goodman on carbon dioxide elimination from SCUBA with standard and modified canisters of the U.S. Navy closed-circuit oxygen rig, (Research Report 1-64, Project F-011-06, Task 3380, Test 6) 1 May 1964. The second report, also by Goodman is entitled: Carbon dioxide absorption systems for SCUBA. 1) I. Quantitative considerations of design and performance of cylindrical canisters, (Research Report 3-64, Project F-011-06-03, Task 3380, Test 8), 15 February 1965. The third of these reports is by M. W. Goodman and T. W. James and is entitled: Carbon dioxide absorption systems for SCUBA. 2) II. Theory and application of a novel, non-cylindrical low resistance carbon dioxide absorption canister for SCUBA, (Research Report 4-65, Project F-011-06-05, Task 11511, Sub-task 4, Report No. 2), 15 June 1965.

2606. **Adriani, J.** Disposal of carbon dioxide from devices used for inhalational anesthesia. *Anesthesiology*, 1960, 21: 742-758.

2607. **Brown, E. S.** Voids, pores and total air space of carbon dioxide absorbents. *Anestehsiology*, 1958, 19: 1-6.

2608. **Brown, E. S.** Performance of absorbents: continuous flow. *Anesthesiology*, 1959, 20: 41-44.

2609. **Brown, E. S. and J. O. Elam.** Practical aspects of carbon dioxide absorption. *N.Y. St. J. Med.*, 1955, 55: 3436-3442.

2610. **Derrick, W. S. and R. C. Smart.** Observations on the carbon dioxide absorption properties of monoethanolamine. *Anesthesiology*, 1957, 18: 551-558.

2611. **Duffner, G. J.** Canister design criteria of carbon dioxide removal from SCUBA. U.S. Navy. EDU, Naval Weapons Plant, Washington, D.C. *Project NS 186-200, sub task no. 4, test no. 44*, 8 March 1957, 12 pp.

2612. **Elam, J. O.** Channeling and overpacking in carbon dioxide absorbers. *Anesthesiology*, 1958, 19: 403-404.

2613. **Gadomski, S.** The absorption and removal of carbon dioxide in the alkali (sodium) sulfate process. pp. 129-135 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by R. R. Miller and V. R. Piatt. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5465*, April 1960, 167 pp.

2614. **Gadomski, T. S.** The use of versene to improve MEA performance. pp. 50-51 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by V. R. Piatt and E. A. Ramskill. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5630*, July 1961, 134 pp.

2615. **Gillen, H. W.** An evaluation of the use of Baralyme in the submarine escape appliance. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 002 015.08, Rept. no. 1*, 1956.

2616. **Goan, J. C.** Alkazid M as a regenerative carbon dioxide absorbent. pp. 92-100 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by R. R. Miller and V. R. Piatt. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5465*, April 1960, 167 pp.

2617. **Goan, J. C.** Alkazid M. p. 52 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by V. R. Piatt and E. A. Ramskill. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5630*, July 1961, 134 pp.

2618. **Huseby, H. W. S. and E. J. Michielsen.** Carbon dioxide absorbent evaluation and canister design. U.S. Navy. EDU, Naval Weapons Plant, Washington, D.C. *Project NS 186-202, sub task no. 2, test no. 14*, 6 November 1959, 33 pp.

2619. **Leonard, J. M.** Algae and submarine habitability. pp. 143-150 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by R. R. Miller and V. R. Piatt. U.S. Navy. Naval Research Laboratory, Washington, D.C., *NRL Rept. 5465*, April 1960, 167 pp.

2620. McConnaughey, W. E. and W. N. Crofford, III. Shipboard tests of carbon dioxide scrubber on USS Nautilus (SSN571). U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Memo Rept. 585*, April 1956, 28 pp.

2621. Miles, G. and J. Adriani. Carbon dioxide absorption. *Anesth. Analg.*, 1959, 38: 293-300.

2622. Miller, R. R. Lithium hydroxide and soda lime as CO<sub>2</sub> absorbents for naval use. pp. 81-87 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by R. R. Miller and V. R. Piatt. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5465*, April 1960, 167 pp.

2623. Miller, R. R. Comparison of carbon dioxide removal systems. pp. 31-36 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by H. W. Carhart and V. R. Piatt. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 6053*, December 1963, 65 pp.

2624. Ravner, H. and C. H. Blachly. Studies on monoethanolamine (MEA). pp. 45-50 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by V. R. Piatt and J. C. White. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5814*, August 1962, 97 pp.)

2625. Ravner, H. and C. H. Blachly. Monoethanolamine stability studies. pp. 25-30 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by H. W. Carhart and V. R. Piatt. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 6053*, December 1963, 65 pp.

2626. Smith, S. H., Jr. Carbon dioxide scrubbing with an alkaline amine solution. pp. 88-91 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by R. R. Miller and V. R. Piatt. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5465*, April 1960, 167 pp.

## F. OXYGEN GENERATORS

For the most part the oxygen supply for modern nuclear submarines is derived from liquid oxygen sources. Other possible sources of oxygen supply are discussed in the references listed below.

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2628. Christian, J. G. Hopcalite-catalyzed combustion. pp. 60-64 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by H. W. Carhart and V. R. Piatt. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 6053*, December 1963, 65 pp.

2629. Gadowski, S. T. and A. L. Pitman. The sulfate-cycle system. pp. 6-9 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by H. W. Carhart and V. R. Piatt. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 6053*, December 1963, 65 pp.

2630. Miller, R. R. Weight economics of carbon dioxide and oxygen equipment for closed spaces. pp. 39-45 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by V. R. Piatt and E. A. Ramskill. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5630*, July 1961, 134 pp.

2631. Musick, J. K. and P. R. Gustafson. Chlorate candles. pp. 29-38 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by V. R. Piatt and E. A. Ramskill. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5630*, July 1961, 134 pp.

2632. Musick, J. K. and P. R. Gustafson. Chlorate candles. pp. 35-43 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by V. R. Piatt and J. C. White. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRC Rept. 5814*, August 1962, 97 pp.

2633. Pitman, A. L. An electrolytic cell for the production of oxygen and sodium hydroxide. pp. 136-142 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by R. R. Miller and V. R. Piatt, U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5465*, April 1960, 167 pp.

2634. Pitman, A. L. and S. T. Gadowski. Laboratory scale operation of the sulfate cycle for carbon dioxide removal and oxygen generation. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5714*, January 1962, 12 pp.

2635. Roach, C. G. and R. W. Roundy. Present status of aircraft liquid oxygen breathing systems. *J. Aviat. Med.*, 1958, 29: 898-902.

2636. Roxburgh, H. L. Some physiological requirements of oxygen systems. *Proc. roy. Soc.*, 1954, 143: 17-24.

2637. Smith, S. H., Jr. Chlorate oxygen candles. pp. 119-122 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by R. R. Miller and V. R. Piatt. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5465*, April 1960, 167 pp.

2638. White, J. C. Electrolytic generation of oxygen. pp. 123-127 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by R. R. Miller and V. R. Piatt. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5465*, April 1960, 167 pp.

2639. Work, G. W. Electrolytic generation of oxygen without the accompanying generation of hydrogen. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 4775*, June 1956, 9 pp.



2640. Young, J. A., R. C. Clark and K. D. Lawrence. Diaphragms for the sulfate-cycle electrolytic cell. pp. 16-20 in: *The present status of chemical research in atmosphere purification and control on nuclear-powered submarines*. Edited by V. R. Piatt and J. C. White. U.S. Navy. Naval Research Laboratory, Washington, D.C. *NRL Rept. 5814*, August 1962, 97 pp

### III. RESUSCITATION

In a variety of situations in submarine operations, diving and in compressed air work the need for resuscitation may arise. The following list of references has been selected to provide the reader with a source of information on this subject.

2641. Elam, J. O., D. G. Greene, E. S. Brown and J. A. Clements. Oxygen and carbon dioxide exchange and energy cost of expired air resuscitation. *J. Amer. med. Ass.*, 1958, 167: 328-334.

2642. Frumin, M. J., N. A. Bergman and D. A. Holaday. Effects of altered expiratory pressures or resistances upon arterial oxygen saturation during artificial respiration. *Fed. Proc.*, 1957, 16: 42.

2643. Gordon, A. S., C. W. Frye, L. Gittelsohn, M. S. Sadove and E. J. Beattie, Jr. Mouth-to-mouth versus manual artificial respiration for children and adults. *J. Amer. med. Ass.*, 1958, 167: 320-328.

2644. Holaday, D. A., J. Israel, E. K. Williams and M. J. Frumin. Variations in ventilation blood flow ratios during artificial respiration. *Fed. Proc.*, 1957, 16: 60.

2645. Ruben, H. E., J. O. Elam, A. M. Ruben and D. G. Greene. Investigation of upper airway problems in resuscitation. 1. Studies of pharyngeal x-rays and performance by laymen. *Anesthesiology*, 1961, 22: 271-279.

2646. Safar, P. Ventilatory efficacy of mouth-to-mouth artificial respiration. *J. Amer. med. Ass.*, 1958, 167: 335-341.

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# Selection and Training of Submarine Personnel, Divers and Compressed Air Workers

## 1. SELECTION

The purpose of selection procedures is to identify predictably those applicants for submarine and diving duty who will succeed in training and perform creditably. As Wise (2676) 1963, has pointed out with regard to aptitude selection standards for the U.S. Navy's First Class Diving Course, the establishment of selection standards based on research would in all probability reduce the attrition rates currently encountered in training. Wise undertook a correlational analysis of 137 records of recent graduates of the diving course as well as failures. This analysis was undertaken to determine what tests within the Navy's basic test battery—general classification index (GCT), mechanical comprehension test (MECH), arithmetic test (ARI), and clerical test (CLER)—could best be utilized as predictors of training success. As determined by a multiple correlation value of 0.428 the combination of ARI and MECH provided the best result. A combined cut-off score of 80 on these tests was suggested as a requirement for entrance in the First Class Diver's Course. As specified by the U.S. Navy the selection requirements for the Deep Sea Divers School are: a) to volunteer for training, b) to pass a physical examination, c) to be interviewed by a qualified diving officer, d) to meet first class swimmer requirements, and e) make a test dive in a diving suit. Using these selection criteria the school has had an attrition rate in 1960–1962 of approximately 20 percent among enlisted men. Of this 20 percent approximately 52 percent are classified as academic failures, 41 percent voluntarily withdrew and the

remaining 7 percent were medically disqualified. For similar comments on submarine personnel selection and assessment reference number 2668, 1956, should be consulted. The interview constitutes an important part of the selection procedure and its reliability as a screen and selection technique has been studied by several, including Crissy and Pashalian (2650) 1952. When conducted by an experienced submarine officer the assessment interview should offer considerable information of predictive value. King (2654, 2656) 1957 and 1959, has published studies on correlates of disqualification in the submarine service and also prediction of Submarine School attrition from the Minnesota Multiphasic Personality Inventory. This investigator studied differences in the response and test scores of a disqualified group and of a qualified group. The two groups were found to be differentiated by a number of variables. The disqualified subjects were inferior in their attendance at the Submarine School and had a lower final standing. They also had a lower Navy GCT (General Classification Index) as well as arithmetic and clerical scores. The data suggested a significantly higher incidence of personality maladjustment in the disqualified group. The two groups were also characterized by different opinions and feelings towards the submarine service. King comments that his studies do not appear to call for changes in current assessment and selection procedures. Kinsey and Weybrew (2659) 1953, have made a descriptive analysis of disqualified submarine personnel from 1947–1952 with the object of determining the major etiological factors



contributing to disqualification. Although quite tentative major conclusions from this investigation were that more than half of the reasons for disqualification could be defined as motivational, the results indicate that some people are disqualified as a result of an inadequate need or motivational pattern as the onset; others are disqualified from the inability, even though optimally motivated at the onset, to reach important goals and to maintain optimal motivation. The Navy Test Battery, especially the GCT and the combined GCT and ARI, was believed by Kinsey and Weybrew to be doing a fairly effective job of screening aptitudinally deficient people from the submarine service. The relationship of these scores to the criterion of disqualification is probably high. The authors feel that patterns of neurotic symptoms are useful predictors of disqualification, but their data were too incomplete in this study to estimate the relationship. Useful assessment predictors might be found by means of dimensioning some one or several of these neurotic variables. Finally, several background factors—education, time in service, previous academic records, and others—were shown to be quite possibly related to the criterion, while job histories, criminal records, etc. were probably not predictive. Kinsey, in a study of psychological aspects of the “Nautilus” transpolar cruise, has commented on the value and characteristics of leadership, as operationally experienced in submarines. This leadership depends not only upon the personality of the leader but upon the varying reactions of the group and of the environment as a whole. Kinsey comments that selection and promotion systems of the U.S. Navy have built-in factors which tend to assure sound leadership. That the assessment and selection, as well as training programs for submarine service, are effective, according to the author, is manifested by the achievement of the officers and men of the “Nautilus”.

The selection and training of divers and underwater swimmers are equally important matters. Miles (2661) 1962, comments that most professional diving schools have a training attrition rate of more than 50 percent. Certain respiratory characteristics, such as slow and deep breathing, as well as capacity for long distance running seems to be highly correlated with suc-

cess in diving training. Mention is also made of the correlation between training failure and inadequate temperamental adaptation. Motivation undoubtedly plays an important role! For further studies on predictors of success in training in submarine school, papers by Weybrew (2669, 2670, 2674) 1954, 1957 and 1959 should be consulted. Youniss (2677) 1956, carried out an investigation of motivation for submarine duty and its relation to submarine school success. Differences in responses to a motivational questionnaire were examined between various levels of achievement in submarine school between Navy rates and between drop-outs and graduates. The most significant differences in motivation occurred between drop-outs and graduates from submarine school, the former being characterized by low initial motivation, lack of interest and a reduced level of aspiration. From these results it appeared that a well designed motivation questionnaire might provide a means of pre-selecting volunteers with adequate motivation and other personality characteristics typical of those who are later dropped from submarine school. An interesting paper is that by Youniss (2678) 1959, on the relationship of tattoos to personal adjustment among enlisted submarine school volunteers. A study was made to compare enlisted men who had tattoos with those who did not in terms of their level of personal adjustment, as indicated by scores on a personality questionnaire. It was found that men with multiple tattoos are less well adjusted than those with none or those with a single tattoo. Moreover, those who desire to obtain tattoos in the future demonstrate less adequate adjustment than those who have no intention of being tattooed. The results of this study seem to indicate that there is a psychological significance in tattoos and in addition these studies contribute to an understanding of a relatively unexplored aspect of human behavior. It should not be claimed that the behavioral factor of having been tattooed is alone sufficient to delineate or identify qualities of personality adjustment.

For a general background study of the occupational problems encountered in submarines a paper by Alvis (2648) 1957, should be read. This article surveys physical and psychological screening, as well as special testing of vision and

hearing. In discussing psychological standards the author comments that the idea that submariners and divers must be the most normal of normal men is not correct. For both the occupation of submariner and diver one must search out special types of men. The identification and description of these men has been most difficult and remains difficult. In the field of deep sea diving it has been possible to proceed by the cull-and-reject method because the number of replacements required were relatively small. Psychometric testing has generally been quite successful in predicting success as defined by completing the submarine school course, however, relating this successful prediction to later success in the submarine force in action has been more difficult. One of the most interesting methods of establishing a desirable and an undesirable characteristic of submariners has been the method of peer rating, in which submariners describe what they like about other submariners they regard highly and what they dislike about those they regard less highly. From the qualities enumerated in such inquiries one may partially describe a submariner in terms of confidence in his ability, recognition of his limitations, dependability and willingness to concede the appropriate social status to his shipmates. Ideally the submariner is a person who does not "freeze up" or "fall apart" in crises, and who does not stand aloof from the group. These definitions are applicable to many men who would not care to the submariners. In addition, a submariner must have enthusiasm for doing the unusual without its being manifested in foolhardy or socially unacceptable behavior. He must be willing to pit his wits against the calculated risk; he must have a zest for accomplishment which overrides creature comfort, at least at times of duty. From the foregoing it is obvious that the recluse, the timid, and the slow witted must be diverted to some other field of operation and endeavor.

A general survey of the literature on selection leads conclusively to the need for unified and more imaginative effort leading to more effective pre-selection and screening of submarine applicants. A more general and open examination of statistics regarding personnel breakdown in the nuclear boats would be highly desirable so as

to determine associations between the present selection techniques and performance outcome.

**2648. Alvis, H. J.** Submarine medicine—an occupational specialty *New Engl. J. Med.*, 1957, 256: 21-25.

**2649. Briggs, D. L., B. Lyon, H. B. Molish and R. R. Deen.** Selected socio-cultural factors affecting interpersonal relations as revealed by the Blacky pictures. I. Discrimination between "unsuitable" and "normal" recruits. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.52, Rept. no. 1*, 22 June 1953.

**2650. Crissy, W. J. E. and S. Pashalian.** The interview: III. Aids to the interview—the submarine stereotype. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 002 016.01, Rept. no. 3*, 20 October 1952.

**2651. Duffner, G. J.** Crew selection for submarine duty. *U.S. Forces med. J.*, 1954, 5: 1192-1198.

**2652. Eysenck, H. J.** A dynamic theory of anxiety and hysteria. *J. ment. Sci.*, 1955, 101: 28-51.

**2653. Foster, R. J. and J. G. Carnaghan.** Prediction of submarine school success through the use of selected themes in the Navy thematic apperception test: U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.54, Rept. no. 1*, 2 May 1955.

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**2656. King, B. T.** Predicting submarine school attrition from the Minnesota Multiphasic Personality Inventory. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Rept. no. 313*, 20 August 1959, 25 pp.

**2657. Kinsey, J. L.** Psychologic aspects of the "Nautilus" transpolar cruise. *U.S. Forces med. J.*, 1959, 10: 451-462.

**2658. Kinsey, J. L. and H. B. Murphree.** Claustrophobic reactions to some stresses of the submarine service. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041.53, Rept. no. 2*, 4 April 1955.

**2659. Kinsey, J. L. and B. B. Weybrew.** Etiological factors in the disqualification of submarine personnel. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 003 041. 13.03*, 22 June 1953, 40 pp.

**2660. McCabe, F. J.** The interview: II. Aids to the interview—the confidential questionnaire. U.S. Navy. Submarine Base, New London, Conn. Medical research laboratory. *Project NM 002 016.01, Rept. no. 2*, 15 October 1952.



2661. Miles, S. Selection and training of divers and underwater swimmers. pp. 244-253 in: *Underwater medicine*. J. B. Lippincott Co., Philadelphia, 1962, 328 pp.

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## II. PERFORMANCE—SUBMARINE OPERATIONS

The period of World War II generated conditions under which there was obvious opportunity to recognize varying degrees of performance quality under stress. The patrols of the Polaris submarines do impose great stress at the present time, nevertheless, the literature on performance in submarines has become reduced in the past few years. Performance data have been collected from various operational activities including the simulated submergence, "Operation Hideout" carried out at the Submarine Base, New London, Connecticut. Among the several reports based on this test, one by Eron and Auld (2680) 1954, may be cited. This particular study was an attempt to discover whether the Hideout population was any different from a random sample of submarine enlisted personnel, and what the effect of confinement aboard a submarine for more than 30 days might be on the results of the Thematic Apperception Test (TAT) and on certain sentence completion tests. By comparison of two items taken from the personal history forms of 100 randomly selected submariners and of the Hideout group, it was found that there was no significant difference between the two samples in age of subject or education of the father (the latter item being used as an index

of the social status of the family). The two samples were significantly different in the formal aspect of the stories they told, with the Hideout subjects becoming less emotionally involved in the task, and in general not cooperating as well as the normative subjects. The incomplete sentences revealed that the motivations of the two groups were different: the normative group seemed to contain significantly more individuals who felt some social responsibility, and significantly fewer individuals who wanted to avoid "messy" details. Between the first and second testing it was apparent that the subjects became increasingly uncooperative, more apathetic, more desirous of leaving and showed heightened sexual phantasies. Increased references to sickness and ill-health were also noted in the completions, as well as an increasing concern over whether or not they were doing the right thing in relation to their peers. For a review and critique of the literature on vigilance performance, reports by McGrath, Harabedian and Buckner (2683) 1959, and Buckner, Harabedian and McGrath (2679) 1960, and Harabedian, McGrath and Buckner (2682) 1960, should be consulted. These papers are also concerned with individual differences in vigilance performance and the probability of signal detection in a vigilance task as a function of intersignal interval. Factors in decline of performance efficiency, especially over periods of time, the effects of display characteristics, the effects of signal characteristics in general, effects of procedural conditions, physiological factors in vigilance performance, motivational differences and methods of improving performance are all discussed. The authors point out the immediate need to investigate performance under operational conditions, also to examine the reliability of individual difference results. The first of these papers is especially valuable in that there is an annotated bibliography.

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**2682. Harabedian, A., J. A. McGrath and D. N. Buckner.** Human factor problems in anti-submarine warfare. Technical Report 3. The probability of signal detection in a vigilance task as a function of intersignal interval. U.S. Navy. Office of Naval Research, Washington, D.C. *NONR 2649(00) NR 153-199*, February 1960, 30 pp.

**2683. McGrath, J. J., A. Harabedian, and D. N. Buckner.** Human factors research in anti-submarine warfare. Technical Report I. Review and critique of the literature on vigilance performance. U.S. Navy. Office of Naval Research, Washington, D.C. *NONR 2649(00) NR 153-199*, December 1959, 100 pp.

### III. HUMAN FACTORS IN ENGINEERING DESIGN

A number of factors in the environment affect vigilance, as Mackworth (2597) 1957, has pointed out. Vigilance may be defined as a state of readiness to detect and respond to certain specific small changes occurring at random time intervals in the environment. The factors in the working situation causing loss of vigilance may be outlined as follows: a) The frequency of the signal. The more frequent the signal the more likely it is to be observed. b) The intersignal interval. Performance is better with a regular interval which is probably the most important factor in determining whether or not there will be a decline in the probability of detection as time goes on. c) The length of the working period. There is a decrement after a half-an-hour, but this depends on a number of physical and psychological factors. It would be useful to know the shortest rest period effective in restoring vigilance. d) Duration of the signal. Decrements may occur with short or longer duration. One must consider unwanted signals also. Research is needed on regularity, frequency and similarity to the wanted signal. There are also general environmental effects, such as noise, heat, isolation and other factors, which can reduce watchfulness. Motivational effects are also to be considered. Loss of sleep may produce reduced motivation, and alertness can be sustained by motivation through giving the subject a small dose of amphetamine sulfate or benzadrine one hour before starting the task. The use of amphetamines demands caution.



For reports of biasing attention during a vigilance task, papers by Baker (2684, 2685) 1956, 1958, may be consulted. Experiments are described in which the subjects were asked to search visual displays and report appearance, at any location on the display, of a spot of light which persisted for one second. On displays with or without a rotating radial line, it was found that subjects detect fewer such spots of light near the periphery of the display. By modifying a radar-like display in order to facilitate a changed pattern of visual search it was demonstrated that more peripheral spots could be detected. Spatial factors in check reading of dial groups have been considered by Lincoln and Averbach (2696) 1956. Papers by Broadbent (2687, 2689) 1952, 1955, may be consulted for studies of responses to one of two synchronous messages. Jones may be consulted (2694) 1960, for studies of fatigue effect in radio operators during a program of high intensity long duration flying. The basic flying unit was a 15 hour sortie divided into five hour watches. The subjects were given a set hourly task, their achievement being scored as its percentage completion in each hour. The experiment was designed to allow examination of results in relation to three different time scales, namely from hour to hour within a watch, from watch to watch within a sortie, and from sortie to sortie within the eight day trial. Optimum duration of watch for a signaller on radio operator duty in flight was found to be three hours, a consistent reduction in measured activity, associated with subjective deterioration becoming manifest after this time. The penalty for exceeding this duration tended to increase as the sortie progressed. There was a progressive decrease in mean level of activity from watch to watch throughout the standard sortie, a decline which it is contended could be partially offset by introducing appropriate rest schedules during long flights. Changes from one sortie to the next, although statistically significant, were not progressive. It was suggested by the author that the results were masked by beginning and end effects.

Changes occurring over the three time scales mentioned are discrete and must be separately measured for useful interpretation of results.

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# Special Psychological and Psychiatric Problems

## I. DUTY AND REST PERIODS

Adams and Chiles (2701) 1960, designed a study to investigate the effect on performance of four different work-rest schedules (two hours on and two hours off, four hours on and four off, six hours on and six off, and eight hours on and eight off) followed over a period of 96 hours. The subject sample consisted of 16 male college students with four subjects being assigned to each of the four work-rest period schedules. Performance was measured by means of a battery of psychomotor tasks involving arithmetic computation, pattern discrimination, monitoring and vigilance. Additional data were obtained from information recorded in an experimenter's log book from responses to a subjective questionnaire administered at the end of the testing. Although the performance tasks failed to differentiate among the four experimental groups, the observational evidence suggested that the subjects in the two hour and four hour groups achieved a more favorable adjustment than those in the other two groups. The selection of optimum work-rest periods may be aided by knowledge of diurnal variations in physiological processes. For example, Buskirk and Iampietro (2703) 1956, measured diurnal variations in resting metabolism during several large field studies to ascertain reasonable base line values for oxygen consumption in any given hour and to ascertain the impact of environment on resting metabolism. Eight men were studied for at least ten days in each of four climates. Weather conditions ranged from hot-dry at Yuma, Arizona to cold-dry at Fort Churchill, Manitoba, Canada. The subjects subsisted on standardized rations during each experiment. Oxygen consumption was routinely measured at 8:00 a.m. (pre-breakfast), noon

(pre-lunch), 4:00 p.m. (pre-supper), and 8:00 p.m. each day after 30 minutes rest in a supine position. Oxygen consumption at 8:00 a.m. was significantly lower than at any other hour. The noon and 4:00 p.m. values were not different from each other, but the 8:00 p.m. value was significantly higher than that at any other hour in each environment. A major portion of the elevation in metabolism during the day was associated with the specific dynamic action. Thus when men fasted and exercised moderately or fasted with no exercise the daily elevation in metabolism was present but was significantly less than when food was given. Prior moderate exercise had little measurable effect on the resting oxygen consumption. The same pattern of results was observed in each environment. It was concluded that the diurnal pattern of oxygen consumption is little affected by environment within the range studied.

Physiological 24 hour rhythms have been studied by Halberg (2705) 1962. The endogenous circadian adaptive functional organization in time affects an animal's ability to withstand environmental damage and has an important bearing upon experimental method. Thus Navy recruits on "four-on" and "eight-off" schedules for two weeks did not show the bimodality of the diurnal temperature curve as previously found in submarine crews on the same schedule.

According to Lehmann (2706) 1962, 3:00 a.m. is found to be a period of low efficiency in man and this is lessened if preceded by a good sleep but it is enhanced by fatigue. Like the pulse frequency all other hemodynamic factors are subject to rhythmical fluctuations over the 24 hour period. Among mental workers who prefer working nights and among night workers in industry there is never a reversed rhythm estab-



lished. It takes four to five days to adjust to a new shift in shiftwork. The biological cycles represent fluctuations of the neuro-vegetative tonus which varies between a predominantly ergotropic (sympathicotonic state) and a predominantly trophotropic phase (parasympathetic state). A gradual change from a 24 to a 20 hour cycle will not seriously affect physiological functions as rapid changes will (i.e. in airline pilots and crew). In submarines the primary timegivers are replaced by regular and strong secondary ones such as 24 hour rhythm in lighting and temperature regulation.

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## II. SLEEP DEPRIVATION

### A. PHYSIOLOGICAL EFFECTS

Hasselman, Schaff and Metz (2721) 1960, have reported the effects of sleep deprivation on urinary excretion of catecholamines in normal human subjects. During a night period before work adrenaline excretion was significantly higher during sleep deprivation than during normal sleep, however, the noradrenaline excre-

tion increase was statistically insignificant. During the work period catecholamine secretion was much higher than during the preperiod night session. The increase of catecholamine excretion caused by lack of sleep was less evident at high temperatures than at low temperatures. Catecholamine excretion proved significantly lower during postperiod sleep than during the work period, but remained somewhat higher than the preperiod level. In a study of the effect of sleep deprivation on plasma 17-hydroxycorticosteroids, Murawski and Crabbé (2734) 1960, deprived eighteen male college students of sleep for one night on two separate occasions. On each occasion each student was alone. On a third occasion students were asked to stay up all night in groups of four. Plasma concentrations of 17-hydroxycorticosteroids at eight o'clock in the morning following the nights without sleep were four to five micrograms lower than control values (significant at the 0.01 level). The noon values after sleep deprivation in a solitary setting were not significantly different from the corresponding values. When subjects stayed up with three other people the noon values tended to be higher. Urinary 17-hydroxycorticosteroid levels showed a decrease following the nights without sleep, but this decrease did not reach statistical significance (between the 0.10 and 0.05 levels). Sharp, Slorach and Vipond (2743) 1961, have concluded that ketosteroid excretory rhythm may depend immediately, and ketogenic steroid rhythm ultimately, on habit and environment. Evidence is presented that ketogenic steroid rhythm is dependent upon synchronization of pituitary and adrenal responsiveness. During reversal of rhythm, adrenocortical activity takes place initially in the early evening and night, occurring progressively earlier each day until it synchronizes with the new time scale. Suzuki (2745) 1961, studied the effects of curtailed sleep on serum cholesterol and on the blood glutathione. These effects were studied on five healthy medical students who had three or six hours sleep in successive four or six days respectively. The subjects did light mental work every day for two hours in the morning and for three hours in the afternoon. During four days before, and one or three days after insufficient sleep, the subjects slept as long as nine

hours. Daily food intake was generally equal in all subjects during the period of nine hours sleep, and in addition a light midnight meal was given during the period of insufficient sleep. The blood for cholesterol analysis was drawn at 8:10 to 8:20 in the morning; for glutathione it was drawn at 8:10 to 8:20 a.m. and at 5:10 to 5:20 p.m. every day. The serum cholesterol rose remarkably before and at the beginning of insufficient sleep and was correlated with the high fat diet. It was slightly lowered or remained almost unchanged in the latter half of the insufficient sleep. Esterified cholesterol levels rose significantly before and in the beginning of insufficient sleep and there was no significant change thereafter. The percentage of ester form to total cholesterol showed remarkable rises in the beginning of insufficient sleep, and was diversely variable thereafter in each subject. The glutathione level of the blood was noticeably lowered after three or four days of insufficient sleep, but this fall was rapidly restored. The results suggested to the authors that the secretion of adrenocortical hormone was accelerated during insufficient sleep.

In a report on the effects of sleep deprivation on body temperatures, Kreider (2726) 1961, has stated that although most earlier work reports little effect of sleep deprivation on body temperature, recent studies indicate that deprivation results in a lowering of deep body temperature. Kreider conducted a study to assess the effects of sleep deprivation on diurnal variation of body temperature and to determine the effect of deprivation on body temperatures during cold stress. Eight men went without sleep for periods up to 87 hours. Skin temperature and rectal temperature were measured periodically at 80°F. during 22 hours of the day, while during the remaining two hours subjects were exposed at 60°F. Following sleep deprivation the men slept for 8 hours in sleeping bags at 10°F. Control measurements were made under identical conditions without deprivation. During sleep deprivation there was a consistently lowered rectal temperature of 0.5–0.7° which persisted throughout the succeeding period of sleep. Rectal temperature at 80°F. and at 60°F. returned to normal after one night of sleep. Skin temperature changed little under all conditions, except toe

temperature which decreased at 80°F. but increased at 60°F. exposure during both wakefulness and sleep following deprivation. Changes in toe temperature were found to be of the same direction and magnitude as observed for cold acclimatization. Murray, Williams and Lubin (2736) 1958, measured body temperature as well as ratings of sleepiness and fatigue from 15 subjects during 98 hours of sleep deprivation. Body temperature showed a persisting diurnal variation, but also indicated an over-all decrease with succeeding hours of sleep deprivation. Self-ratings of sleepiness and fatigue and sleepiness ratings by fellow subjects and observers, were positively intercorrelated as well as positively correlated with increasing hours of sleep loss. The four ratings and body temperature were inversely correlated, even when hours of sleep deprivation were partialled out. The subjects tended to rate themselves as less sleepy than the observers rated them, which was interpreted as an adjustment mechanism. It was concluded by the authors that the results support Kleitman's hypothesis that reports of sleepiness are inversely related to body temperature. Schaff and Marbach (2739) 1960, conducted experiments to determine the action on "quantity of sleep" of fatigue states of different degrees brought about during the preceding day by various combinations of 1) environmental temperature, 2) muscular work, 3) sleep deprivation. Spontaneous movements of the sleeper were used as an indication of the depth or quantity of sleep. The results showed that only sleep deprivation had any significant effect upon the quantity of sleep. The muscular work level and the environmental temperature level did not significantly influence spontaneous motility during sleep. Nor was any interaction between the three factors shown to be significant. The effect of sleep deprivation upon the logarithm of the total number of movements per night, however, was clearly apparent.

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## B. EFFECTS OF SLEEP DEPRIVATION ON PERFORMANCE

In general sleep deprivation tends to impair performance. As Ax, Fordyce, Loovas, Meredith, Pirojnikoff, Shmavonian and Wendahl (2749) 1954, have stated, however, human beings tend to compensate psychophysiologically for the fatigue of sleep deprivation by increased effort or efficiency. The degree of compensation is a function of motivation during performance. In a study of the effects of sleep loss on performance, reported by Wilkinson (2759) 1958, an effort was made to define more precisely the task situation in which performance is likely to be impaired by moderate sleep loss, that is to say some 30 hours without sleep. A wide variety of task situations was examined in the course of eight experiments and in two of them sleep loss pronounced decline of efficiency. The first of these task situations was a 40 minute vigilance situation essentially similar to the job of a radar or asdic lookout. In performance tasks the effect of sleep loss on efficiency did not become apparent until at least 10 minutes had been spent on the task. Individuals differed considerably in the degree of effect shown. In a number of short tasks lasting less than 10 minutes, no significant decline in efficiency was observed after sleep loss. These short tasks included tests of learning and sorting ability, and tests which allowed comparison between tasks having high positive or large negative transfer of skill from past training. The author's results seem to suggest that only prolonged tasks will be effected by sleep loss. It has been shown as a result of the experiments that if the task situation is reorganized in such a way as to give the subject more information of the results of his efforts, the performance decrement due to sleep loss may be substantially removed. In conclusion it appears that the less predictable the sleepless operator finds the task situation, the greater the penalty he suffers for failing to predict it accurately,

the less likely he is to let his efficiency fall below normal levels. Loveland and Singer (2753) 1959, have concluded that personality structure as reflected in projective tests, is unaltered by acute sleep deprivation and personality functioning is little changed. Using the Rorschach test alone it was possible to predict how well a subject would remain efficient in a variety of mental and psychomotor tasks during a sleep deprivation period, and also whether or not he would hallucinate. Subjects whose Rorschach showed high motivation tended to maintain or raise the efficiency levels on re-test. Others showed decrement. Those subjects who reported hallucinations were usually those characterized by loosely defended, hysteric-like style of adapting and those with prominent schizophrenic traits. Loveland and Williams (2754) 1963, had 20 experimental and 20 control subjects (soldiers from 18 to 45 years of age and of average Army intelligence) add pairs of one-digit numbers for three minutes at 8:00 a.m. and at 8:00 p.m. during a three day baseline period, during three days of sleep loss and two days of recovery. The most marked effect of sleep loss was to lower the speed of addition. The speed during the afternoon was higher than in the morning and this difference tended to increase with sleep loss but not significantly. Accuracy was high throughout all test sessions with a slight decrease during sleep loss. It was not affected by the diurnal cycle and did not correlate with oral temperature. The correlation of speed of addition and oral temperature was considerably higher than that of speed and sleep loss. Behavioral changes during sleep loss have been reported by Luby, Frohman, Grisell, Lenzo and Gottlieb (2755) 1960. The effect of sleep deprivation upon behavior, thinking, motor performance and biological energy transfer systems was studied in a single subject who remained awake without drugs for 200 hours. Behavioral changes included irritability, paranoid thinking, expansiveness, grandiosity, hypnagogic states, visual hallucinations and episodic rages. Defects in thinking and in visual motor performance occurred cyclically across days of wakefulness with gradual deterioration, finally resulting in virtual untestability on the ninth day. The effects of sleep deprivation on



social behavior have been reported by Murray, Schein, Erikson, Hill and Cohen (2756) 1959. During two separate experiments with 72 and 98 hours of sleep deprivation, observations were made of the social, recreational and general behavior of the subjects. Categories included social conversation, games, television, reading, hobbies and non-participation. The strongest and most significant finding was that with sleep deprivation the subjects tended to change restlessly from one activity to another. Work on hobbies and in crafts decreased during the sleep deprivation period. Social conversation, of a listless sort, showed an over-all increase with sleep deprivation, although the exact shape of the relationship cannot be specified. The authors' results were interpreted as indicating that the subjects made efforts to maintain wakefulness by avoiding situations producing drowsiness.

It has been confirmed that 30 hours of sleep loss can seriously impair performance toward the end of a 25 minute task of serial reaction. Particularly, the occurrence of gaps or abnormally long response delays is greatly increased. This is what happens when the test is a continuous one; when 30 seconds rest pauses were allowed (Wilkinson (2761) 1959) every five minutes the above effect of lack of sleep was found to remain unaltered. An equal though small and insignificant improvement in performance occurred under both normal and sleep deprived conditions with the rest pauses.

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## C. EFFECTS OF DRUGS AND SLEEP DEPRIVATION

Carlson (2768) 1961, found that after 47 and 71 hours of sleep deprivation there was overestimation in judgment of size of objects. This also occurred after 200 mg. of chlorpromazine and the administration of placebos. Kornetsky, Mirsky, Kessler and Dorff (2769) 1959, have tested normal subjects after 44 and 68 hours of sleep loss with and without simultaneous administration of dextro-amphetamines. Ten milligrams of the drug were given at 44 hours and 15 mg. at 68 hours. The authors' result support the

conclusions that sleep loss produces a greater decrement in some psychological performances than in others; also, measures of performances which reflect "lapses" seem to be more affected than measures which are relatively insensitive to lapses. Dextro-amphetamine returns only the least impaired performances to the non-sleep deprived level. Measures of performances sensitive to lapses still differs significantly from the non-sleep deprived level.

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### III. ISOLATION, SENSORY DEPRIVATION AND CONFINEMENT

The references that follow represent a selection of pertinent papers dealing with problems that may be useful to the reader concerned with prolonged isolation and confinement in submarine operations. Closely related are the problems that may be encountered by the underwater swimmer resulting from partial sensory deprivation. Since there are many unknown variables in this important area, a plea is made for well-designed and prosecuted research studies of both a basic and applied nature.

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# Special Problems of Scuba Diving

## I. GENERAL STUDIES

In contrast to the conventional diver connected to the surface by means of his air line, the SCUBA diver has the advantage of freedom of movement and stealth. These attributes allow men to perform a variety of tasks which can be accomplished by other means only with great difficulty if at all. The military use of SCUBA has included the penetration of harbor defenses and the sinking of large warships, the reconnaissance of beachheads, the clearing of underwater obstacles before and after assaults and the location and disposal of mines. Diving with SCUBA is an expanding field of practical endeavor, not only for military purposes, but also for use in scientific submarine explorations, oceanographic studies and in marine biological research activities.

Since most of the problems encountered in SCUBA diving are also experienced in conventional diving with the hard hat a full discussion of these problems will not be presented here. These problems have been discussed in the foregoing sections. The expanded civilian interest in and participation in SCUBA diving has been followed by an expanded literature on medical problems of shallow water diving. Of especial interest are papers by: Duffner (2814), Lanphier (2822), Taylor (2884) and reports 2853 and 2854.

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## II. NERVOUS SYSTEM

Many investigators have shown that air at raised barometric pressures exerts certain mental and psychomotor effects on man such as euphoria, confusion, slowed mental activity, motor incoordination and impairment in performance. Roger, Cabarro and Gastaut (2876) studied the electroencephalogram in 12 well-trained divers who were exposed to a pressure of 10 atmospheres absolute. Records were taken immediately before and during the pressure exposure. There was an augmentation of frequency, a decrease in amplitude, and the potentials evoked by photic stimuli were augmented in amplitude.

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## III. CARDIOVASCULAR SYSTEM

Diving animals gradually develop a marked bradycardia which in most cases is of sinus origin. Pulse rate may decrease and the bradycardia once developed persists during physical activity and struggle. The bradycardia and shifting blood flow, together with the hypoxia and hypercapnia, indicate that submersion has pronounced effects upon the cardiovascular system. Scholander, Hammel, LeMessurier, Hemmingsen and Garey (2884) 1961, studied 31 native skin divers in Australia. Of these, the blood lactate remained normal in five divers, but also showed an acute rise in the recovery period. The authors have indicated that this asphyxial defense seems well developed at birth, and an acute rise of lactic acid after the first cry has recently been described by other investigators.

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## IV. RESPIRATION

Deep sea divers recognize a reduced ability to hyperventilate at several atmospheres ambient



pressure. Since there is a need for deep diving operations by the U.S. Navy and the need for heavy work during such dives, it is important to know the limitations imposed upon the human respiratory apparatus. A comparison by Goff and Bartlett (2892) in 1957 of the respiratory response of trained versus untrained swimmers to the exercise involved in underwater swimming revealed that end-tidal carbon dioxide levels were elevated in the trained swimmers. The breathing pattern in the trained swimmers (slow deep breaths with long post-inspiratory pauses) might have accentuated the large cyclic variation in alveolar  $P_{CO_2}$  accompanying the respiratory cycle during exercise, thus resulting in an elevated endtidal  $P_{CO_2}$  without elevated alveolar or arterial  $P_{CO_2}$ . The authors suggested that the increase in the average alveolar  $P_{CO_2}$  might have been partially the result of a significantly lower oxygen ventilation equivalent in the trained swimmers as compared to the non-trained subjects.

Carey, Schaefer and Alvis (2890) in 1956 compared lung volumes of laboratory personnel with those of escape training tank instructors. Vital capacities were found to be significantly larger in the tank instructors. Longitudinal studies of the lung volumes of instructors carried out for a period of one year following their assignment to an escape training tank exhibited a significant increase in total lung capacity, vital capacity, inspiratory reserve and tidal volume.

Lanphier (2896) 1955, reported abnormal carbon dioxide levels, as measured with an end-tidal gas sampler in divers. The levels were accompanied by corresponding abnormalities in the acid-base equilibrium. A definite difference from the norm appeared to be a characteristic in certain divers. Carbon dioxide sensitivity tests were also conducted in the same subjects, and these tests correlated with the carbon dioxide tensions observed in these men under various conditions. Although a definite relationship between carbon dioxide sensitivity and the phenomenon in question was noted, the probable utility of a standard sensitivity test as a personnel selection procedure remains uncertain.

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## V. KIDNEY

Utilizing complete water immersion, Grave-line and Jackson (2902) recorded the diuretic response of five human subjects immersed in water for six hours. Their results demonstrated a lowered specific gravity diuresis which had the characteristics of both a water and an osmotic diuresis.

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## VI. OXYGEN CONSUMPTION

As might be expected the work of moving air through the breathing apparatus will be increased as the ambient pressure is increased. This effect is due primarily to the increased density of the gas and to the respiratory resistance of the specific breathing apparatus. Lanphier (2909) in 1954 measured the oxygen requirements of underwater swimmers using SCUBA gear, and recorded the influence of speed and other factors on swimming efficiency. Oxygen consumption was determined at swimming speeds between 0.5 and 1.2 knots in 15 subjects. The results indicated that efficiency decreased progressively above 0.8 knots. At this speed the average trained swimmer required 1.3 liters of oxygen per minute. Individual variations and the influence of training and body size were found to be considerable. Goff, Frassetto and Specht (2907) in 1956 carried out similar experiments on underwater swimmers. The average oxygen consumption was 1.3 to 1.9 liters per minute at average swim rates from 0.7 to 0.9 miles per hour. A wide variation in oxygen consumption was observed. This range was not narrowed when converted to liters of oxygen per square meter of body surface and the authors attributed these differences to individual swimming ability. Frequent subjective symptoms of carbon dioxide accumulation in the breathing apparatus were reported.

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## VII. SPATIAL ORIENTATION

The exposure of the underwater swimmer to water in which the illumination is considerably limited may impose on the swimmer a weightless environment similar to that experienced by the astronaut in space flight. Beckman, Coburn, Chambers, DeForest, Augerson and Benson (2911) in 1961 immersed seven subjects in water up to the neck level for periods of five to 23 hours and recorded a significant weight loss during the immersion period. This is explained by the diuresis which occurred. A decrease in expiratory reserve volume and in respiratory minute volume was also recorded during the immersion period.

The ability to orient to the vertical during water immersion was investigated by Brown (2913) in 1961. The subjects were immersed in water at a depth of either 18 or 25 feet and then rotated in a tucked position on a rod through three, four or five revolutions. Rotation was terminated with the head in one of four positions: upright, inclined forward, down or back. Upon termination of rotation the subjects were directed to point in the up direction and then to swim to the surface. There were errors in direction of initial pointing of as much as 180 degrees. Errors were greatest with the head down or back, and least with the head up or forward. Nodding of the head was followed by consistent improvement in the direction of pointing. There was little indication of any difficulty in swimming in the upward direction. A greater density of the legs as compared to the trunk resulted in fairly rapid vertical orientation of the body upon release of the rod. The results were interpreted to reflect the relative inefficiency of the utricles as gravity sensors when the head is in certain positions.

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## VIII. HAZARDS FROM DANGEROUS FISH AND OTHER MARINE ORGANISMS

Swimming in tropical waters exposes the underwater swimmer to marine life which on many occasions inflicts wounds or stings which can be as serious as the results of shark attack. For a general review of problems related to dangerous fish and other marine organisms the reader should consult reports of Halstead (2934) 1959, Keegan and Macfarlane (2939) 1963, Miles (2942) 1962, Ravina and Ravina (2945) 1959, and by the U.S. Navy (2953) 1956.

Among the marine animals that produce wounds the most generally feared are sharks. There are more than 225 species of sharks, but only a score or more are believed to attack men. It is difficult to make specific statements concerning the actual risk of attacks by sharks

since as a whole the experience of divers indicates that the risk is almost negligible but the possibilities exist. Danger of shark attacks is greatest in tropical and sub-tropical seas. Particularly dangerous areas are Queensland, Australia and South Africa. Most attacks have occurred when the temperature of the water was greater than 70°F., however, sharks feed at all hours and particularly at night. Sharks are attracted by blood, carrion, flashing of light, colored materials, thrashing about, explosions or unusual noises. When they are hunting in packs and food or blood is present sharks become highly excited and may radically alter their usual habits. It is at times like this that the greatest danger is encountered and that "shark repellents" are useless. Sharks will frequently single out an individual in a crowd and will ignore others who may attempt to rescue him; several men together, however, are in a better position to ward off sharks than is a lone swimmer. It has been demonstrated that if the individual is not wounded the shark may leave if he remains perfectly still.

Generally dark colored equipment and clothing are preferred to light colored articles. The use of explosives can easily be expected to attract sharks in large numbers. The fatality rate from actual shark attack has been estimated at more than 80 percent. Bites are severe. Death is due to massive bleeding and shock. Gilbert (2933) 1960, has stated that attempts to wound the shark are usually useless and may even aggravate the situation, but if such action appears necessary, hit the shark on the snout, eyes or gills. It may be necessary to actually shove the shark away with the use of a "shark billy"—a large stick carried for this purpose—or with some other object. For additional references on shark attack papers by Miles (2942) 1962, Coppleson (2928) 1958, Gilbert (2932) 1960, and Tester (2952) 1958, should be consulted. Poisonous scorpion fish can be found in all tropical and temperate seas. One of the most dangerous species under this classification is the stonefish (*Synanceja horrida*). This species carries venomous spines on the back and about the tail. Wiener (2954) 1958, has stated that both local and general effects may follow the sting of a stonefish. The local effects are pain, swelling, paralysis and

loss of sensation of the injured limb. The general effects include repeated syncope, impairment of all sensations, involvement of respiration and coma. Abscess formation, necrosis and gangrene not uncommonly complicate the local effects of a sting and delay convalescence. Dyspnea and general weakness may last for several months after a sting. The author recommends that a tourniquet be applied immediately and this should be followed by scrubbing of the wound with water, incision and suction. The wound area should be infiltrated with a solution of one grain of emetin hydrochloride per millilitre. Alternatively, and when the use of emetin is contraindicated, 0.1 to 0.5 millilitre of a five percent solution of potassium permanganate may be used. Prophylactic injections of penicillin and immunization against tetanus are required in severe cases of injury.

When stonefish venom is administered intravenously, rabbits (Austin, Carincros and McCallum (2925)) show hypotension, respiratory distress and muscular paralysis. Experimental evidence indicates that the systemic effects are due to the powerful myotoxic properties of the venom which produce cardiac paralysis and conduction block in involuntary and skeletal muscle. The authors suggest that this conduction block is due to a slow depolarization of the muscle and that the cause of death is due to paralysis of the diaphragm.

There are many varieties of rays and many of them are venomous. The exact nature of the venom apparatus varies from species to species, but it usually consists of a spine covered by a skin-like sheath. The spine is located on the upper side of the tail and a variable distance from the base of the tail. Stingrays are generally found lying on the bottom in shallow water; they are usually well-camouflaged and are often partly covered by sand. The main danger to a swimmer or diver is that of stepping on one. When stepped on the ray strikes upward with its tail and drives the spine deeply into the foot or leg. The venom produces severe pain and if present in large quantities can cause generalized effects. For a report of an unusual injury to the liver by a barbed stingray a paper by Cadzow (2926) 1960, should be consulted.

A difficult condition to diagnose is the dermatitis produced by marine parasites, sea urchins and seaweed. For general references on the subject papers by the following should be consulted: Arnold (2923) 1958, Arnold and Bonnet (2924) 1950, Chu (2927) 1952, Cort (2929) 1950, Hutton (2937) 1960, Leigh (2940 and 2941) 1953 and 1955, Moschella (2943) 1951, Rocha and Fraga (2946) 1962, Sams (2947) 1949, Strauss (2949) 1956, Stunkard and Hinchcliffe (2950) 1952, Zinn (2955) 1954, and Temine and Coulier (2951) 1961.

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## IX. UNDERWATER BREATHING APPARATUS

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# Key to Abbreviations of Journals and Handbooks Cited

- Acta biol. med., Germ.* Acta Biologica et Medica Germanica. Berlin.
- Acta cardiol., Brux.* Acta cardiologica. Bruxelles.
- Acta chir. orthop. traum. Cech.* Acta Chirurgiae Orthopaedicae et Traumatologiae Cechoslovaca. Praha.
- Acta chir. scand.* Acta chirurgica Scandinavica. Stockholm.
- Acta endocr., Copenhagen.* Acta endocrinologica. Copenhagen.
- Acta med. hung.* Acta medica Academiae scientiarum hungaricae. Budapest.
- Acta med. scand.* Acta medica Scandinavica. Stockholm.
- Acta morph. neerl.-scand.* Acta morphologica Neerlandico-Scandinavica. Utrecht.
- Acta oto-laryng., Stockh.* Acta otolaryngologica. Stockholm.
- Acta paediatr., Stockh.* Acta paediatrica. Stockholm, Uppsala.
- Acta path. microbiol. scand.* Acta pathologica et microbiologica Scandinavica. Kjobenhavn.
- Acta physiol. lat. amer.* Acta physiologica Latino Americana. Buenos Aires.
- Acta physiol. pharm. neerl.* Acta physiologica et pharmacologica Neerlandica. Amsterdam.
- Acta physiol. scand.* Acta physiologica Scandinavica. Stockholm.
- Acta psychiat., Kbh.* (see *Acta Psychiat., scand.*).
- Acta psychiat. scand.* Acta psychiatrica Scandinavica. Kjobenhavn.
- Acta psychol., Hague.* Acta psychologica. Hague.
- Acta radiol., Stockh.* Acta radiologica. Stockholm.
- Acta Soc. Med., Uppsala.* Acta Societatis medicorum Upsaliensis. Uppsala.
- Advanc. Sci., Lond.* Advancement of Science. London.
- Aeromed. Acta.* Aeromedica Acta. Soesterberg.
- Aerospace Med.* Aerospace Medicine. Washington.
- Arztl. Forsch.* Arztliche Forschung. Bad Worishafen.
- Arztl. Wschr.* Arztliche Wochenschrift. Berlin.
- A.I.B.S. Bull.* American Institute of Biological Sciences. Washington.
- Air Univ. Quart. Rev.* Air University Quarterly Review. Montgomery, Washington.
- Amer. chem. Soc. J.* (see *J. Amer. chem. Soc.*).
- Amer. Col. Surg., clin Conf.* (see *Surg. Forum*).
- Amer. Heart J.* American Heart Journal. St. Louis.
- Amer. ind. Hyg. Ass. J.* American Industrial Hygiene Association Journal. Chicago.
- Amer. J. Bot.* American Journal of Botany. Lancaster, Pa.
- Amer. J. Dis. Child.* American Journal of Diseases of Children. Chicago.
- Amer. J. Cardiol.* American Journal of Cardiology. New York.
- Amer. J. clin. Path.* American Journal of Clinical Pathology. Baltimore.
- Amer. J. Hyg.* American Journal of Hygiene. Baltimore.
- Amer. J. Med.* American Journal of Medicine. New York.
- Amer. J. med. Sci.* American Journal of the Medical Sciences. Philadelphia.
- Amer. J. med. Tech.* American Journal of Medical Technology. Detroit.
- Amer. J. Nurs.* American Journal of Nursing. Philadelphia.
- Amer. J. Obstet. Gynec.* American Journal of Obstetrics and Gynecology. St. Louis.
- Amer. J. Ophthal.* American Journal of Ophthalmology. St. Louis.
- Amer. J. Optom.* American Journal of Optometry. Minneapolis.
- Amer. J. Path.* American Journal of Pathology. Boston.
- Amer. J. phys. Med.* American Journal of Physical Medicine. Baltimore.
- Amer. J. Physiol.* American Journal of Physiology. Boston.
- Amer. J. Psychiat.* American Journal of Psychiatry. Baltimore.
- Amer. J. Psychol.* American Journal of Psychology. Worcester.
- Amer. J. Roentgenol.* American Journal of Roentgenology (Radium Therapy and Nuclear Medicine). New York.
- Amer. J. Surg.* American Journal of Surgery. New York.
- Amer. Psychol.* American Psychologist. Lancaster, Pa.
- Amer. Rev. resp. Dis.* American Review of Respiratory Diseases. Baltimore.
- Anaesthesia.* Anaesthesia. London.
- Anaesthesist.* Anaesthesist. Berlin.
- Analyt. Chem.* Analytical Chemistry. Easton, Pa.
- Anat. Rec.* Anatomical Record. Philadelphia.
- Anesth. Analg.* Anesthésie et analgésie. Paris.
- Anesth. Analg. curr. Res.* Anesthesia and Analgesia Current Researches. Elmira, N.Y.
- Anesthesiology.* Anesthesiology. Lancaster, Pa.
- Ann. Chir. Gyn. Fenn.* Annales chirurgiae et gynaecologiae Fenniae. Helsinki.
- Ann. intern. Med.* Annals of Internal Medicine. Ann Arbor.
- Ann. Med. nav. trop.* Annali di medicina navale e tropicale. Roma.

- Ann. N.Y. Acad. Sci.* Annals of the New York Academy of Sciences. New York.
- Ann. occup. Hyg.* Annals of Occupational Hygiene. London.
- Ann. Otol., etc., St. Louis.* Annals of Otolology, Rhinology and Laryngology. St. Louis.
- Ann. Paedit. Fenn.* Annales paediatricae Fenniae. Helsinki.
- Ann. pharm. franç.* Annales pharmaceutiques françaises. Paris.
- Ann. Surg.* Annals of Surgery. Philadelphia, London.
- Annu. Rev. Med.* Annual Review of Medicine. Stanford University. Palo Alto.
- Annu. Rev. Physiol.* Annual Review of Physiology. Stanford University. Palo Alto.
- Appl. Ther.* Applied Therapeutics. Toronto.
- Arch. Biochem.* Archives of Biochemistry and Biophysics. New York.
- Arch. bras. Cardiol.* Archivos brasileiros de cardiologia. São Paulo.
- Arch. Chir. Neerl.* Archivum chirurgicum Neerlandicum. Arnhem.
- Arch. Derm.* Archives of Dermatology. New York.
- Arch. envir. Hlth.* Archives of Environmental Health. Chicago.
- Arch. exp. Path. Pharmak.* Naunyn-Schmiedeberg's Archiv für experimentelle Pathologie und Pharmakologie. Leipzig.
- Arch. gen. Psychiat.* Archives of General Psychiatry. Chicago.
- Arch. Gewerbepath.* (see *Int. Arch. Gewerbepath.*).
- Arch. industr. Hlth. Hyg.* (see *Arch. envir. Hlth.*).
- Arch. int. Pharmacodyn.* Archives internationales de pharmacodynamie et de thérapie. Bruxelles-Paris, Gand.
- Arch. int. Physiol.* Archives internationales de physiologie et de biochimie. Liège, Paris.
- Arch. intern. Med.* Archives of Internal Medicine. Chicago.
- Arch. Mal. prof.* Archives des maladies professionnelles de médecine du travail et de sécurité sociale. Paris.
- Arch. E. Maragliano.* Archivio E. Maragliano di patologia e clinica. Genova.
- Arch. Neurol.* Archives of Neurology. Chicago.
- Arch. Ophthal.* Archives of Ophthalmology. New York.
- Arch. Otolaryng.* Archives of Otolaryngology. Chicago.
- Arch. Path.* Archives of Pathology. Chicago.
- Arch. phys. Med.* Archives of Physical Medicine and Rehabilitation. Omaha.
- Arch. phys. Ther.* Archiv für Physikalische Therapie, Balneologie und Klimatologie. Leipzig.
- Arch. Surg.* Archives of Surgery. Chicago.
- Arch. Toxikol.* Archiv für Toxikologie. Berlin.
- Arkh. Pat.* Arkhiv Patologii. Moskva.
- Aust. J. exp. Biol. med. Sci.* Australian Journal of Experimental Biology and Medical Science. Adelaide.
- Aviat. Week.* Aviation Week. New York.
- B.C. med. J.* British Columbia Medical Journal. Vancouver.
- Beitr. klin. Chir.* Beiträge zur klinischen Chirurgie. Tübingen.
- Beitr. Klin. Tuberk.* Beiträge zur Klinik der Tuberkulose und Spezifischen Tuberkuloseforschung. Würzburg.
- Beitr. path. Anat.* Beiträge zur pathologischen Anatomie und zur allgemeinen Pathologie. Jena.
- Beitr. Silikose-Forsch.* Beiträge zur Silikose-Forschung. Bochum.
- Biofizika.* Biofizika. Moskva.
- Biol. Bull., Wood's Hole.* Biological Bulletin. Marine Biological Laboratory. Wood's Hole, Mass.
- Biophys. J.* Biophysical Journal. New York.
- Biul. Inst. Med. morsk. Gdansk.* Biuletyn Instytutu medycyny morskiej w Gdąnsku. Warszawa.
- Biul. Eksp. Biol. Med.* (see *Bull. Biol. Med. exp. URSS*).
- Blood.* Blood. The Journal of Hematology. New York.
- Boll. Soc. ital. Biol. sper.* Bollettino della Società italiana di biologia sperimentale. Napoli.
- Brit. Heart J.* British Heart Journal. London.
- Brit. J. Anaesth.* British Journal of Anaesthesia. Manchester.
- Brit. J. Cancer.* British Journal of Cancer. London.
- Brit. J. industr. Med.* British Journal of Industrial Medicine. London.
- Brit. J. Pharmacol.* British Journal of Pharmacology and Chemotherapy. London.
- Brit. J. Psychiat.* British Journal of Psychiatry. London.
- Brit. J. Psychol.* British Journal of Psychology. Cambridge.
- Brit. J. Radiol.* British Journal of Radiology. London.
- Brit. J. Surg.* British Journal of Surgery. Bristol.
- Brit. med. Bull.* British Medical Bulletin. London.
- Brit. med. J.* British Medical Journal. London.
- Brookhaven Symp. Biol.* Brookhaven Symposia in Biology. Upton, N.Y.
- Bull. Acad. nat. Med.* Bulletin de l'Académie nationale de médecine. Paris.
- Bull. Biol. Med. exp. URSS.* Byulleten' eksperimental' noi biologii i meditsiny. Moskva.
- Bull. exp. Biol. Med.* Bulletin of Experimental Biology and Medicine, U.S.S.R. New York. (Eng. trans. of *Bull. Biol. Med. exp. URSS*).
- Bull. Inst. morsk. Med. Gdansk.* (see *Biul. Inst. Med. morsk. Gdansk*).
- Bull. Los Angeles neurol. Soc.* Bulletin of the Los Angeles Neurological Society. Los Angeles.
- Bull. math. Biophys.* Bulletin of Mathematical Biophysics. Chicago.
- Bull. schweiz. Akad. med. Wiss.* Bulletin der Schweizerischen Akademie der medizinischen Wissenschaften. Basel.
- Bull. Soc. int. Chir.* Bulletin de la Société internationale de chirurgie. Bruxelles.
- Bull. Univ. Md. Sch. Med.* Bulletin. Maryland University School of Medicine and College of Physicians and Surgeons. Baltimore.
- Bur. Ships J.* Bureau of Ships Journal. Washington.
- Canad. Anaesth. Soc. J.* Canadian Anaesthetists' Society Journal. Toronto.
- Canad. J. Biochem.* Canadian Journal of Biochemistry. Ottawa.
- Canad. J. Med. Sci.* (see *Canad. J. Biochem., Canad. J. Physiol. Pharmacol.*).
- Canad. J. Physiol. Pharmacol.* Canadian Journal of Physiology and Pharmacology. Ottawa.



- Canad. J. Psychol.* Canadian Journal of Psychology. Toronto.
- Canad. med. Ass. J.* Canadian Medical Association Journal. Toronto.
- Cancer Chemother. Rep.* Cancer Chemotherapy Reports. (National Cancer Inst.) Bethesda.
- Cancer Res.* Cancer Research. Baltimore.
- Chem. Abstr.* Chemical Abstracts. Easton, Pa.
- Circulation.* Circulation. Journal of the American Heart Association. New York.
- Circulation Res.* Circulation Research. New York.
- Clin. Chem.* Clinical Chemistry. Baltimore, New York.
- Clin. Res.* Clinical Research. American Federation for Clinical Research, New York.
- Clin. Sci.* Clinical Science, incorporating Heart. London.
- Clin. Symp.* Clinical Symposia. (CIBA) Summit, N.J.
- Compar. Biochem. Physiol.* Comparative Biochemistry and Physiology. London.
- C. R. Soc. Biol., Paris.* Compte rendu des séances de la Société de biologie. Paris.
- Curr. Res. Anesth.* (see *Anesth. Analg. curr. Res.*).
- Dis. Chest.* Diseases of the Chest. El Paso, Texas.
- Dis. nerv. Syst.* Diseases of the Nervous System. Chicago.
- Dissert. Abstr.* Dissertation Abstracts. Ann Arbor.
- Dtsch. Gesundheitwes.* Das deutsche Gesundheitswesen. Berlin.
- Dtsch. med. J.* Deutsches medizinische Journal. Berlin.
- Dtsch. med. Wschr.* Deutsche medizinische Wochenschrift. Leipzig.
- Dtsch. Versuchsanst. Luftf.* Deutsche Versuchsanstalt für Luftfahrt e.v. — Mülheim (Ruhr). Köln.
- Duodecim.* Duodecim. Kirjoituksia laaketieteen ja laakarin toiminnan aloilta. Helsinki.
- EEG clin. Neurophysiol.* Electroencephalography and Clinical Neurophysiology. Montreal.
- Endocrinology.* Endocrinology. Glendale, Calif.
- Ergonomics.* Ergonomics. London.
- Erie Cty. med. Bull.* Bulletin of the Medical Society, County of Erie, Buffalo.
- Exp. Cell Res.* Experimental Cell Research. New York.
- Exp. Neurol.* Experimental Neurology. New York, London.
- Experientia.* Experientia. Basel.
- Farbe.* Farbe. Goettingen.
- Farmakol. Toksik.* Farmakologiya i Toksikologiya. Moskva.
- Fed. Proc.* Federation Proceedings (American Societies for Experimental Biology). Washington.
- Fertil. Steril.* Fertility and Sterility. New York.
- Fiziol. Zh. SSSR Sechenov.* Fiziologicheskii zhurnal SSSR im. I.M. Sechenov. Leningrad.
- Folia med., Napoli.* Folia medica. Napoli.
- Folia psychiat. neur., jap.* Folia psychiatrica et neurologica japonica. Okayama.
- Fortschr. Röntgenstr.* Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin. Stuttgart.
- France méd.* France médicale. Paris.
- Genetics.* Genetics. Princeton.
- GERS.* Groupe d'Etudes et de Recherches Sous-Marines.
- Gigiiena Sanit.* Gigiena i sanitariya. Leningrad, Moskva.
- G. ital. Tuberc.* Giornale italiano della tubercolosi.
- G.P. G.P.* American Academy of General Practice. Kansas City.
- Harvey Lect.* Harvey Lectures. Philadelphia and London.
- Hefte z. Unfallheilk.* Hefte zur Unfallheilkunde. Leipzig.
- Helv. physiol. acta.* Helvetica physiologica et pharmacologica acta. Basel.
- IEEE Trans med. Electr.* IEEE Transactions on Bio-Medical Electronics. New York.
- Industr. Med. Surg.* Industrial Medicine & Surgery. Chicago.
- Int. Arch. Gewerbepath.* Internationales Archiv für Gewerbepathologie und Gewerbehygiene. Berlin.
- Internist.* Internist. Berlin, Göttingen.
- Int. J. Air Wat. Poll.* International Journal of Air and Water Pollution. London.
- Int. J. Radiat. Biol.* International Journal of Radiation Biology and related Studies in Physics, Chemistry and Medicine. London.
- XXI Int. physiol. Congr.* XXI International Physiological Congress. Leiden.
- XXII Int. physiol. Congr.* XXII International Physiological Congress. Leiden.
- Int. Rec. Med.* International Record of Medicine and General Practice Clinics. New York, Washington.
- Int. Z. angew. Physiol.* Internationale Zeitschrift für angewandte Physiologie einschliesslich Arbeitsphysiologie. Berlin.
- J. abnorm. soc. Psychol.* Journal of Abnormal and Social Psychology. Boston.
- J. acoust. Soc. Amer.* Journal of the Acoustical Society of America. Menasha, Wis.
- J. Albert Einstein med. Cent.* Journal of the Albert Einstein Medical Center. Philadelphia.
- J. Allergy.* Journal of Allergy. St. Louis.
- J. Amer. chem. Soc.* Journal of the American Chemical Society. Easton, Pa.
- J. Amer. geriat. Soc.* Journal of the American Geriatrics Society. Baltimore, Chicago.
- J. Amer. med. Ass.* Journal of the American Medical Association. Chicago.
- J. Amer. osteop. Ass.* Journal of the American Osteopathic Association. Chattanooga, Tenn.
- Jap. J. med. Progr.* Japanese Journal of Medical Progress. Nankodo.
- Jap. J. Physiol.* Japanese Journal of Physiology. Nagoya.
- J. appl. Phys.* Journal of Applied Physics. Lancaster, Pa.
- J. appl. Physiol.* Journal of Applied Physiology. Washington.
- J. appl. Psychol.* Journal of Applied Psychology. Worcester, Mass.
- J. Aviat. Med.* (see *Aerospace Med.*).
- J. biol. Chem.* Journal of Biological Chemistry. Baltimore.
- J. Bone Jt. Surg.* Journal of Bone and Joint Surgery. Boston.
- J. cardiovasc. Surg.* Journal of Cardiovascular Surgery. Torino.

- J. cell. comp. Physiol.* Journal of Cellular and Comparative Physiology. Philadelphia.
- J. Chromatogr.* Journal of Chromatography. Amsterdam, London.
- J. clin. Endocrin.* Journal of Clinical Endocrinology and Metabolism. Springfield, Ill.
- J. clin. exp. Psychopath.* Journal of Clinical and Experimental Psychopathology and Quarterly Review of Psychiatry and Neurology. New York, Washington.
- J. clin. Invest.* Journal of Clinical Investigation. Baltimore.
- J. comp. physiol. Psychol.* Journal of Comparative and Physiological Psychology. Baltimore.
- J. comp. Psychol.* (see *J. comp. physiol. Psychol.*).
- J. Endocrin.* Journal of Endocrinology. Oxford, Cambridge.
- J. environ. Sci.* Journal of Environmental Sciences. Illinois.
- J. exp. Med.* Journal of Experimental Medicine. New York.
- J. exp. Psychol.* Journal of Experimental Psychology. Princeton.
- J. Fla. med. Ass.* Journal of the Florida Medical Association. Jacksonville.
- J. forens. Med.* Journal of Forensic Medicine. Cape Town.
- J. forens. Sci.* Journal of Forensic Sciences. Mundelein, Illinois.
- J. Franklin Inst.* Journal of the Franklin Institute. Philadelphia.
- J. gen. Physiol.* Journal of General Physiology. Baltimore, New York.
- J. Geront.* Journal of Gerontology. Springfield, Ill.
- J. Hered.* Journal of Heredity. Washington.
- J. int. Coll. Surg.* Journal of the International College of Surgeons. Chicago.
- J. Kans. med. Soc.* Journal of the Kansas Medical Society. Columbus.
- J. Lab. clin. Med.* Journal of Laboratory and Clinical Medicine. St. Louis, Mo.
- J. Lancet.* Journal-Lancet. Minneapolis, Minn.
- J. ment. Sci.* (see *Brit. J. Psychiat.*).
- J. Mich. med. Soc.* Journal of the Michigan State Medical Society. Detroit.
- J. Mt. Sinai Hosp.* Journal of the Mount Sinai Hospital. New York.
- J. nat. Cancer Inst.* Journal of the National Cancer Institute. Washington.
- J. nerv. ment. Dis.* Journal of Nervous and Mental Diseases. New York.
- J. Neurochem.* Journal of Neurochemistry. London, New York.
- J. Neuropath. clin. Neurol.* Journal of Neuropathology and Clinical Neurology. Chicago.
- J. Neuropath. exp. Neurol.* Journal of Neuropathology and Experimental Neurology. Baltimore.
- J. Neurophysiol.* Journal of Neurophysiology. Springfield, Ill.
- J. Neuropsychiat.* Journal of Neuropsychiatry. Chicago.
- J. Neurosurg.* Journal of Neurosurgery. Springfield, Ill.
- J. Obstet. Gynaec., Brit. Commonw.* Journal of Obstetrics and Gynaecology of the British Commonwealth. London.
- J. occup. Med.* Journal of Occupational Medicine. Chicago.
- J. opt. Soc. Amer.* Journal of the Optical Society of America. Philadelphia.
- J. Parasit.* Journal of Parasitology. Lancaster, Pa.
- J. Pediat.* Journal of Pediatrics. St. Louis, Mo.
- J. Personality.* Journal of Personality. Durham, N.C.
- J. Pharmacol.* Journal of Pharmacology and Experimental Therapeutics. Baltimore.
- J. phys. Chem., Ithaca.* Journal of Physical (and Colloid) Chemistry. Ithaca, N.Y.
- J. Physiol., Lond.* Journal of Physiology. London and Cambridge.
- J. Physiol., Paris.* Journal de physiologie. Paris.
- J. Physiol. Path. gen.* (see *J. Physiol., Paris*).
- J. project. Tech.* Journal of Projective Techniques. Glendale, Calif.
- J. psychiat. Res.* Journal of Psychiatric Research. London.
- J. R. Inst. publ. Hlth. Hyg.* Journal of the Royal Institute of Public Health and Hygiene. London.
- J. R. nav. med. Serv.* Journal of the Royal Naval Medical Service. London.
- J. Sci. Labour.* Journal of the Science of Labour. Tokyo.
- J. soc. Psychol.* Journal of Social Psychology. Worcester, Mass.
- J. Speech Dis.* Journal of Speech and Hearing Disorders. Columbus, O.
- J. thorac. cardiovasc. Surg.* Journal of Thoracic and Cardiovascular Surgery. St. Louis, Mo.
- J. thorac. Surg.* (see *J. thorac. cardiovasc. Surg.*).
- J. trop. Med. Hyg.* Journal of Tropical Medicine and Hygiene. London.
- Klin. Med., Mosk.* Klinicheskaya Meditsina. Moskva.
- Klin. Wschr.* Klinische Wochenschrift. Berlin.
- Konink. Ned. Akad. Wetenschap.* Koninklijke Nederlandse Akademie van Wetenschappen. Amsterdam.
- Lab. Invest.* Laboratory Investigation. International Academy of Pathology. New York.
- Lancet.* Lancet. London.
- Lang. Arch. klin. Chir.* Langenbecks Archiv für klinische Chirurgie. Berlin.
- Laryngoscope, St. Louis.* Laryngoscope. St. Louis.
- Life Sci.* Life of Science. Krakow.
- Lyon chir.* Lyon Chirurgical. Lyon.
- Maroc méd.* Maroc médical. Casablanca.
- Marseille méd.* Marseille médical. Marseille.
- Méd. aéro.* Médecine aéronautique. Paris.
- Med. Arts Sci.* Medical Arts and Sciences. Washington.
- Medd. flyg. o. navmed. Namnd.* Meddelanden från Flyg- och Navalmedicanska Namnden. Stockholm.
- Med. Exp.* Medicina Experimentalis. Basel, New York.
- Medicine, Baltimore.* Medicine. Baltimore.
- Medizinische.* (see *Med. Welt, Stuttgart*).
- Med. J. Aust.* Medical Journal of Australia. Sydney.
- Med. J. Malaya.* Medical Journal of Malaya. Singapore.
- Med. Klinik.* Medizinische Klinik. Herline, Wien.
- Med. d. Lavoro.* Medicina del lavoro. Milano.
- Med. Mschr., Stuttg.* Medizinische Monatsschrift. Stuttgart.
- Med. Sci.* Medical Sciences. Series 7, Progress in Nuclear Energy. London.
- Med. Serv. J., Can.* Medical Services Journal, Canada. Ottawa.



- Med. Sport.* Medicina sportiva. Torino.
- Med. Tech. Bull.* Medical Technicians Bulletin. Washington.
- Med. Welt, Stuttg.* Medizinische Welt. Stuttgart.
- Med. World, Lond.* Medical World. London.
- Med. World News.* Medical World News. New York.
- Milit. Med.* Military Medicine. Washington.
- Milit. med. J.* Military Medical Journal (Eng. trans. of *Vo.-med. Zh.*) Washington.
- Milit. Surg.* (see *Milit. Med.*).
- Militaerlaegen.* Militaerlaegen. Kjobenhavn.
- Minerva cardioangiol.* Minerva cardioangiologica. Torino.
- Minerva fisioter.* Minerva fisioterapia. Torino.
- Minerva med., Roma.* Minerva medica. Roma.
- Minn. Med.* Minnesota Medicine. St. Paul.
- Modern Med., Minneap.* Modern medicine. Minneapolis.
- Mtschr. Unfallheilk. VersichMed.* Monatsschrift für Unfallheilkunde und Versicherungsmedizin. Berlin-Wilmersdorf.
- Münch. med. Wschr.* Münchener medizinische Wochenschrift. München.
- Nature, Lond.* Nature. London.
- Nature, Paris.* Nature. Paris.
- Naunyn-Schmiedebergs Arch. exp. Path. Pharmak.* (see *Arch. exp. Path. Pharmak.*).
- N.C. med. J.* North Carolina Medical Journal. Winston-Salem.
- Ned. milit.-geneesk. Tijdschr.* Nederlands militair geneeskundig tijdschrift.
- Ned. Tijdschr. Geneesk.* Nederlandsch tijdschrift voor geneeskunde. Amsterdam.
- Neurology, Minneap.* Neurology. Minneapolis.
- Nevropat. i Psikh.* Nevropatologiya i psikhiatriya. Moskva.
- New Engl. cardiovasc. Soc.* New England Cardiovascular Society.
- New Engl. J. Med.* New England Journal of Medicine. Boston.
- New Scient.* New Scientist. London.
- Nisshin Igaku.* (see *Jap. J. med. Progr.*).
- Nord. med.* Nordisk Medicin. Stockholm.
- N.Y. St. J. Med.* New York State Journal of Medicine. New York.
- N.Z. med. J.* New Zealand Medical Journal. Wellington.
- Occup. Psychol.* Occupational Psychology. London.
- Ohio St. med. J.* Ohio State Medical Journal. Columbus.
- Operat. Res.* Operations Research Society of America. Baltimore, Bethesda.
- Pacif. Sci.* Pacific Science. Honolulu.
- Panminerva med.* Panminerva medica. Torino.
- Patol. Fiziol. éksp. Terap.* Patologicheskaya fiziologiya i éksperimental'noya terapiya. Moskva.
- Path. Biol.* Pathologie et biologie. Paris.
- Pediatrics, Springfield.* Pediatrics. Springfield, Ill.
- Pediatrica.* Pediatriya. Moskva.
- Percept. Mot. Skills.* Perceptual and Motor Skills. Louisville.
- Pflüg. Arch. ges. Physiol.* Pflügers Archiv für die gesamte Physiologie des Menschen und der Tiere. Bonn.
- Pharmacol. Rev.* Pharmacological Reviews. Baltimore.
- Pharm. & Toxic.* (see *Farmakol. Toksik.*).
- Physiologist, Wash.* Physiologist. Washington.
- Physiol. Rev.* Physiological Reviews. Baltimore.
- Phys. Med. Biol.* Physics in Medicine and Biology. London.
- Phys. Ther. Rev.* (see *Physical Therapy*). New York.
- Postgrad. Med.* Postgraduate Medicine. Milwaukee.
- Practitioner.* Practitioner. London.
- Pr. méd.* Presse médicale. Paris.
- Probl. Virol.* Problems of Virology. New York, London. (Eng. trans. of *Voprosy virusologii*. Moskva).
- Proc. Hawaii. Acad. Sci.* Proceedings. Hawaiian Academy of Science. Honolulu.
- Proc. Mayo Clin.* Proceedings of Staff Meetings of the Mayo Clinic. Rochester, Minn.
- Proc. nat. Acad. Sci., Wash.* Proceedings of the National Academy of Sciences of the United States of America. Washington.
- Proc. roy. Soc.* Proceedings of the Royal Society. London.
- Proc. R. Soc. Med.* Proceedings of the R. Society of Medicine. London.
- Proc. Soc. exp. Biol., N. Y.* Proceedings of the Society for Experimental Biology and Medicine. New York.
- Prog. Biophys. biophys. Chem.* Progress in Biophysics and Biophysical Chemistry. London.
- Psychiat. et Neurol. jap.* Psychiatria et neurologia japonica. Tokyo.
- Psychiat. Quart.* Psychiatric Quarterly. Albany, Utica.
- Psychiat. Res. Repts.* Psychiatric Research Reports. Washington.
- Psychol. Monogr.* Psychological Monographs. Lancaster, Pa. Washington.
- Psychol. Rev.* Psychological Review. Lancaster, Pa.
- Psychosom. Med.* Psychosomatic Medicine. Washington, Philadelphia.
- Quart. J. exp. Physiol.* Quarterly Journal of Experimental Physiology. London.
- Quart. J. exp. Psychol.* Quarterly Journal of Experimental Psychology. Cambridge.
- Radiat. Res.* Radiation Research. New York.
- Radiology.* Radiology. St. Paul.
- Rass. clin.-scient. Ist. biochim. ital.* Rassegna clinico-scientifica dell'Istituto biochimico italiano. Milano.
- Rev. Agressol.* Revue d'Agressologie. Paris.
- Rev. Cps. Santé Armées.* Revue des Corps de santé des armées, terre, mer, air. Paris.
- Rev. Cps. Santé milit.* (see *Rev. Cps. Santé Armées*).
- Rev. Czech. Med.* Review of Czechoslovak Medicine. Prague.
- Rev. Franç. clin. biol.* Revue française d'études cliniques et biologiques. Paris.
- Rev. Laryng., Paris.* Revue de laryngologie, d'otologie et de rhinologie. Paris.
- Rev. méd. Aero, Rio de J.* Revista médica de aeronáutica. Rio de Janeiro.
- Rev. Méd. nav.* (see *Cps. Santé Armées*).
- Rev. Path. comp.* Revue de pathologie générale et de physiologie clinique. Paris.

- Rev. Soc. argent. Biol.* Revista de la Sociedad argentina de biologia. Buenos Aires.
- Rif. med.* Riforma medica. Napoli.
- Riv. Infort.* Rivista degli infortuni e delle malattie professionali. Roma.
- Riv. Med. aero.* Rivista di medicina aeronautica e spaziale. Roma.
- S.A.E. J.* S.A.E. Journal. Society of Automotive Engineers. New York.
- S. Afr. med. J.* South African Medical Journal. Cape Town.
- S.B. ost. Akad. Wiss., Wien.* Sitzungsberichte der Österreichischen Akademie der Wissenschaften. Wien.
- Scand. J. clin. Lab. Invest.* Scandinavian Journal of Clinical and Laboratory Investigation. Oslo.
- Schweiz. med. Wschr.* Schweizerische medizinische Wochenschrift. Basel.
- Sci. Amer.* Scientific American. New York.
- Science.* Science. New York.
- Sci., Ill.* Science Illustrated.
- Sci. Stud.* Science Studies.
- Scot. med. J.* Scottish Medical Journal. Edinburgh, Glasgow.
- Sechenov. J. Physiol. USSR.* Sechenov Physiological Journal of the USSR. New York, London. English trans. of *Fiziol. Zh. SSSR Sechenov*.
- Sem. Hop. Paris.* Semaine des hopitaux de Paris. Paris.
- Spectrum.* Spectrum; an Oxford journal of Science. Oxford.
- Stanf. med. Bull.* Stanford Medical Bulletin. San Francisco, Palo Alto.
- Stud. Cercet. Fiziol.* Studii si cercetări de fiziologie. Bucuresti.
- Surgery.* Surgery. St. Louis.
- Surg. Forum.* Surgical Forum. American College of Surgeons. Philadelphia, Chicago.
- Surg. Gynec. Obstet.* Surgery, Gynecology and Obstetrics. Chicago.
- Svenska Lakartidn.* Svenska Lakartidning. Stockholm.
- Tidsskr. norske Lægeforen.* Tidsskrift for den Norske lægeforening. Kristiana, Kjobenhavn.
- Tohoku J. exp. Med.* Tohoku Journal of Experimental Medicine. Sendai.
- Trans. Amer. Acad. Ophthal. Otolaryng.* Transactions, American Academy of Ophthalmology and Otolaryngology. St. Louis.
- Trans. Amer. neurol. Ass.* Transactions of the American Neurological Association. New York.
- Trans. Amer. Otol. Soc.* Transactions of the American Otological Society. Boston.
- Trans. Amer. Soc. artif. intern. Organs.* Transactions. American Society for Artificial Internal Organs. Washington.
- Trans. Ass. Amer. Phycns.* Transactions of the Association of American Physicians. Philadelphia.
- Trans. ophthal. Soc. U.K.* Transactions of the Ophthalmological Society of the United Kingdom. London.
- Tri-St. med. J.* Tri-State Medical Journal. Shreveport.
- Tr. Leningr. sanit.-gig. med. Inst.* Trudy Leningradskogo sanitarnogigienicheskogo meditsinskogo instituta. Leningrad.
- Trud. Inst. fiziol. I. P. Pavlova.* Trudy Instituta fiziologii imeni I. P. Pavlova. Akademiya nauk SSSR. Moskva.
- Ugeskr. Læg.* Ugeskrift for Læger. Kjobenhavn.
- Univ. Mich. med. Bull.* University of Michigan Medical Bulletin. Ann Arbor.
- U.S. Forces med. J.* United States Armed Forces Medical Journal. Washington.
- Verh. dtsh. Ges. Kreisf. Forsch.* Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung. Dresden, Darmstadt.
- Verh. dtsh. Ges. Path.* Verhandlungen der Deutschen Gesellschaft für Pathologie. Stuttgart.
- Vestn. Akad. med. Nauk., SSSR.* Vestnik Akademii meditsinskikh nauk SSSR. Moskva.
- Vestn. Roentg. Radiol.* Vestnik roentgenologii i radiologii. Leningrad, Moskva.
- Vestn. Otorhinolaryng., Leningr.* Vestnik oto-rino-laringologii. Leningrad, Moskva.
- Virchows Arch.* Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizin. Berlin.
- Vo-med. Zh. (see Milit. med. J.).*
- Vop. Pitani.* Voprosy pitaniya.
- Wien. klin. Wschr.* Wiener klinische Wochenschrift. Wien.
- Wien. med. Wschr.* Wiener medizinische Wochenschrift. Wien.
- Wien Z. inn. Med.* Wiener Zeitschrift für innere Medizin und ihre Grenzgebiete. Wien.
- Wschr. Unfallheilk.* Wochenschrift Unfallheilkunde.
- Zbl. allg. Path. Anat.* Zentralblatt für allgemeine Pathologie und pathologische Anatomie. Jena.
- Zbl. ArbMed. ArbSchutz.* Zentralblatt für Arbeitsmedizin und Arbeitsschutz. Darmstadt.
- Z. ges. inn. Med.* Zeitschrift für die gesamte innere Medizin und ihre Grenzgebiete. Leipzig.
- Zh. Neuropat. Psikh. Korsakov.* (see *Neuropat. i Psikh.*).
- Zh. Vyss. nerv. Deyat. I. P. Pavlova.* Zhurnal vysshei deyatelnosti nervnoi imeni I. P. Pavlova. Moskva.
- Z. Hyg. InfektKr.* Zeitschrift für Hygiene und Infektionskrankheiten. Leipzig, Berlin.
- Z. KreisForsch.* Zeitschrift für Kreislaufforschung. Dresden, Darmstadt.
- Z. Laryng. Rhinol.* Zeitschrift für Laryngologie, Rhinologie, Otologie und ihre Grenzgebiete. Würzburg.
- Z. Orthopad.* Zeitschrift für Orthopädie und ihre Grenzgebiete. Stuttgart.
- Z. Tropenmed. u. Parasit.* Zeitschrift für Tropenmedizin und Parasitologie. Stuttgart.
- Z. Vitam.-Horm.-u. Fermentforsch.* Zeitschrift für Vitamin-, Hormon- und Fermentforschung. Wien.



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